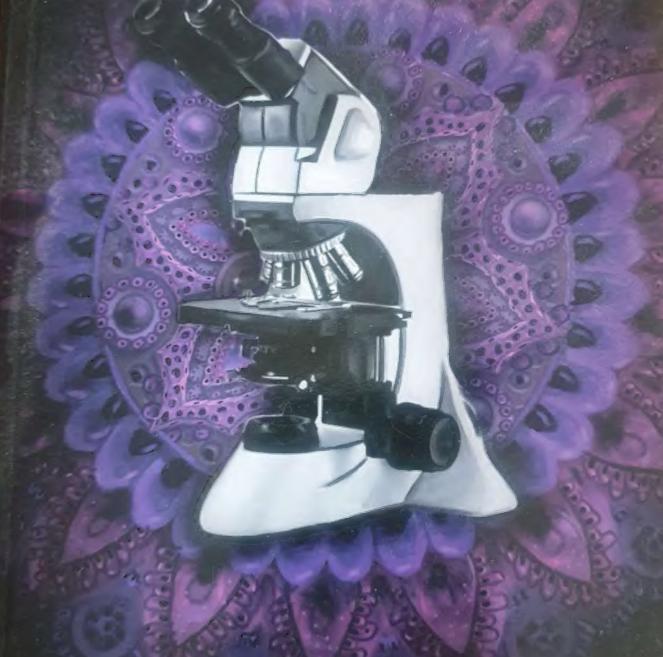
CONCEPT BOUN PATHOLOGY



ACTIVE RECALL BASED



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# CELL AS A UNIT OF HEALTH AND DISEASE

# **CONCEPTS**

- Concept 1.1: Human Genome
- Concept 1.2: Morphogens and Mitogens
- Concept 1.3: Gene Editing

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2 | PATHOLOGY

Concept 1.1: Human College SNP, CNV, MIRNA, LNC RNA, Epigenetics, Cell cycle, growth

factor table, CRISPER

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	30 mins
(* reading	15 mins
published in draft form in 2001 and more co	ompletely detailed in 2003.

 Contains roughly 3.2 billion DNA base pairs. Contains roogin;
 Within the genome there are about 20,000 protein-encoding genes, comprising only

about 1.5% of the genome.

• 80% of the human genome either binds proteins, implying it is involved in regulating gene expression, or can be assigned some functional activity, mostly related to the regulation of gene expression, often in a cell-type specific fashion.

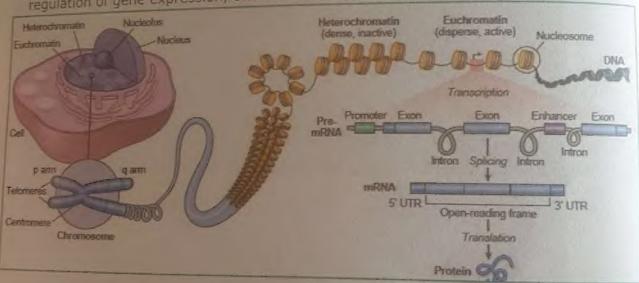


Fig. 1.1

The major classes of functional non-protein-coding sequences found in the human

- 1. Promoter and enhancer regions that provide binding sites for transcription factors.
- 2. Binding sites for factors that organize and maintain higher order chromatin
- 3. Noncoding regulatory RNAs. More than 60% of the genome is transcribed into RNAs that are never translated into protein, but which nevertheless can regulate gene expression through a variety of mechanisms. The two best- studied varieties are micro-RNAs and long noncoding RNAs.
- 4. Mobile genetic elements (e.g., transposons). Remarkably, more than one third of the human genome is composed of these elements, popularly denoted as "jumping genes." These segments can move around the genome, exhibiting wide variation in number and positioning even amongst closely related species (i.e., humans and other primates). They are implicated in gene regulation and chromatin organization, but their function is still not well established.



Special structural regions of DNA, in particular telomeres (chromosome ends) and centromeres (chromosome "tethers").

The person-to-person variation, including differential susceptibility to diseases and in response to environmental agents and drugs, is encoded in less than 0.5% of our DNA. Though small when compared to the total nucleotide sequences, this 0.5% represents about 15 million base pairs.

The two most common forms of DNA variation in the human genome are single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs).

# Concept 1.1.1: Single Nucleotide Polymorphisms (SNPS):

- · Variants at single nucleotide positions and are almost always biallelic (i.e., only two choices exist at a given site within the population, such as A or T).
- · Over 6 million human SNPs have been identified, many of which show wide variation in frequency in different populations.
- SNPs occur across the genome ~ within exons, introns, intergenic regions, and coding
- the SNP and the causative genetic factor are in linkage disequilibrium
- There is hope that groups of SNPs may serve as markers of risk for multigenic complex diseases such as type II diabetes and hypertension

### Concept 1.1.2: Copy Number Variations (CNVS):

- Recently identified form of genetic variation consisting of different numbers of large contiguous stretches of DNA from 1000 base pairs to millions of base pairs.
- CNVs are responsible for between 5 and 24 million base pairs of sequence difference between any two individuals.
- Approximately 50% of CNVs involve gene-coding sequences; thus, CNVs may underlie a large portion of human phenotypic diversity.

EPIGENETICSs: is defined as heritable changes in gene expression that are not caused by alterations in DNA sequence

Different cell types are distinguished by lineage-specific programs of gene expression. Such cell type-specific differences in DNA transcription and translation depend on epigenetic factors (literally, factors that are "above genetics") that can be conceptualized as follows.

- 1. Histones and histone modifying factors.
- Nucleosomes consist of DNA segments
- · 147 base pairs long that are wrapped around a central core structure of highly conserved low molecular weight proteins called histones.
- The resulting DNA-histone complex resembles a series of beads joined by short DNA linkers and is generically called chromatin.
- · At the light microscopic level, nuclear chromatin exists in two basic forms: (1) cytochemical lyden seand transcriptionally inactive heterochromatin and
- (2) cytochemically dispersed and transcriptionally active euchromatin.
- Chromatin remodeling complexes can reposition nucleosomes on DNA, exposing (or obscuring) gene regulatory elements such as promoters.
- "Chromatin writer" complexes, on the other hand, carryout more than
- · 70 different histone modifications generically denoted as marks. Such covalent alterations include methylation, acetylation, or phosphorylation of specific amino acid residues on the histones.



· Histone marks are reversible through the activity of "chromatin erasers." Still other Histone marks are reversible through binding histones that bear particular marks proteins function as "chromatin readers," binding histones that bear particular marks

and thereby regulating gene expression. and thereby regulating games and arginines can b methylated by specific writer

• Histone methylation. Both lysines and arginines can b methylated by specific writer

enzymes.

Histone acetylation. Lysine residues are acetylated by histone acetyl transferases.

Histone acetylation to open up the chromatin and increases.

Histone acetylation. Lysine tend to open up the chromatin and increase transcription.

(HAT), whose modification tend to open up the chromatin and increase transcription. (HAT), whose modification to the reversed by histone deacetylases (HDAC), leading to chromatin condensation. · Histone phosphorylation. Serine residues can be modified by phos- phorylation.

• DNA methylation. High levels of DNA methylation in gene regulatory elements

typically result in transcriptional silencing.

· Chromatin organizing factors. Much less is known about these proteins, which are believed to bind to noncoding regions and control long-range looping of DNA.

### Micro RNA and Long Coding RNA:

Gene regulation also depends on the functions of noncoding RNAs.

As the name implies, these are encoded by genes that are transcribed but not translated. Two important examples are discussed here: small RN molecules called microRNAs, and long noncoding RNA >200 nucleotides in length.

### Concept 1.1.3: Micro RNA (miRNA):

The miRNAs do not encode proteins; instead, they function primarily to modulate the translation of target mRNA into their corresponding proteins.

Posttranscriptional silencing of gene expression by miRNA is a fundamental and wellconserved mechanism of gene regulation present in all eukaryotes (plants and animals). Generation of microRNAs (miRNA) and their mode of action in regulating gene function. miRNA genes are transcribed to produce a primary miRNA (pri-miRNA), which is processed within the nucleus to form pre-miRNA composed of a single RNA strand with secondary hairpin loop structures that form stretches of double-stranded RNA. After this pre-miRNA is exported out of the nucleus via specific transporter proteins, the cytoplasmic Dicer enzyme trims the pre-miRNA to generate mature double- stranded miRNAs of 21 to 30 nucleotides. The miRNA subsequently unwinds, and the resulting single strands are incorporated into the multiprotein RNA-induced silencing complex (RISC). Base pairing between the single-stranded miRNA and its target mRNA directs RISC to either cleave the mRNA target or repress its translation. In either case, the target mRNA gene is silenced post transcriptionally.

Small interfering RNAs (siRNAs) are short RNA sequences that can be introduced experimentally into cells. These serves as substrates for Dicer and interact with the RISC complex in a manner analogous to endogenous miRNAs.

Synthetic siRNAs targeted against specific mRNA species have become useful laboratory tools to study gene function (so-called knockdown technology); they are also being developed as possible therapeutic agents to silence pathogenic genes, such as oncogenes

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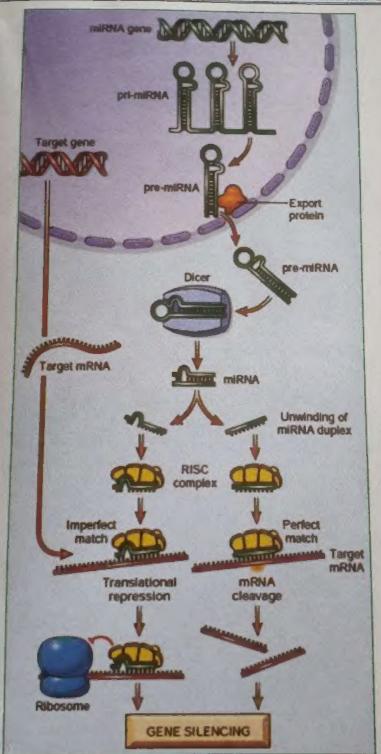


Fig. 1.2

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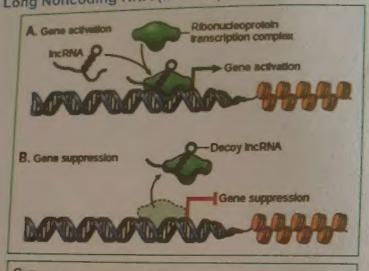
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Concept 1.1.4: Long Noncoding RNA (IncRNA):



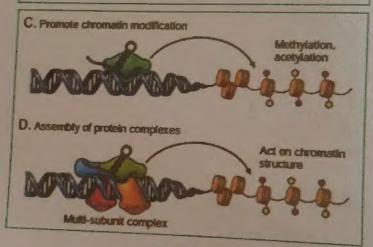


Fig. 1.3

# Roles of long noncoding RNAs.

- A. Long non-coding RNAs (IncRNAs) can facilitate transcription factor binding and thus
- B. conversely, IncRNAs can preemptively bind transcription factors and thus pre- vent
- C. Histone and DNA modification by acety- lases or methylases (or deacetylases and demethylases) may be directed by the binding of IncRNAs.
- D. In other instances, lncRNAs may act as scaffolding to stabilize secondary or tertiary structures and/or multi subunit complexes that influence general chro- matin

The best known example of a repressive function involves XIST, which is transcribed from the X-chromosome and plays an essential role in physiologic X-chromosome inactivation. XIST itself escapes X inactivation, but forms a repressive "cloak" on the X chromosome from which it is transcribed, resulting in gene silencing. Conversely, it has recently been appreciated that many enhancers aresites of IncRNA synthesis, and these IncRNAs appear to often increase transcription from gene promoters through a variety of mechanisms.



# Concept 1.2: Morphogens and Mitogens

Morphogens are proteins that help in development of a tissue / organ Mitogens are protein which induce proliferation (mitosis) of a cell.

## Growth Factors Involved in Inflammation and Repair:

Carindadheta.	feater	Peniction
Epiderma, growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, and many other cells.	Mitogenic for keratinocytes and fibroblasts stimulates keratinocyte migration (morphogenic)
Transforming growth toctor-u (FGF-a)	Activated macrophages, keratinocytes, many other cell types.	Stimulates proliferation (mitogenic) & migration (morphogenic) of hepatocytes and many other epithelial cells.
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells In the liver, endothelial cells.	Enhances proliferation of hepatocytes and other epithelial cells (mitogenic); Increases cell motility(morphogenic).
Vascular endothelial growth factor (VEGI);	Mesenchyme cells.	Stimulates proliferation of endothelial cells; Increases vascular permeability. (morphogenic and mitogenic)
Platelet derived growth (actor PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes.	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis.
throblast growth factors I GEs), Including acidic I GF-1, and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types.	Chemotactic and mitogenic for fibroblasts: stimulates angiogenesis and ECM protein synthesis.
ransforming growth actor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts.	Chemotactic for leukocytes and fibroblasts stimulates ECM protein synthesis; suppresses acute Inflammation, induces cell cycle arrest in G1. (morphogen not mitogen)
eratinocyte growth factor (GL) (i.e., FGF-7)	fibroblasts.	Stimulates keratinocyte migration, proliferation, and differentiation.

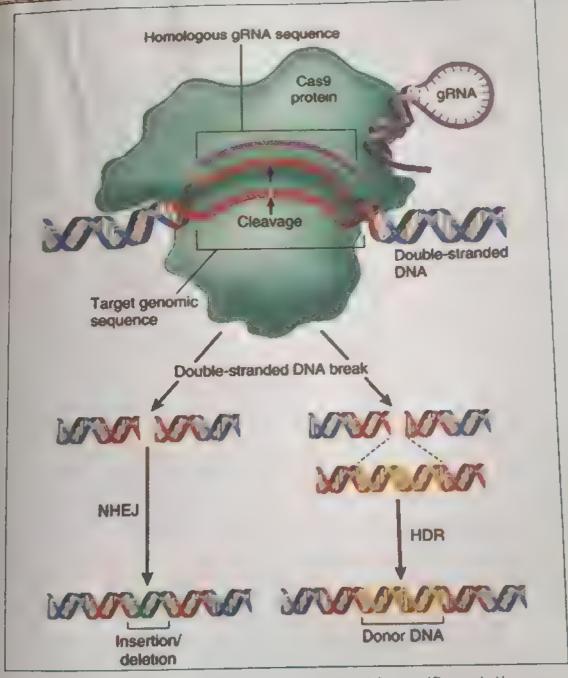
Latest Update From Basics of Pathology, 10th Edition:

membrane

# Concept 1.3: Gene Editing

- Exciting new developments that permit exquisitely specific genome editing stand to usher in an era of molecular revolution. These advances come from a wholy unexpected source: the discovery of clustered regularly interspaced short palindromic repeats (CRISPRs) and Cas (or CRISPR-associated genes).
- These are linked genetic elements that endow prokaryotes with a form of acquired immunity to phages and plasmids.
- Bacter,a use this system to sample the DNA of infecting agents, incorporating it into
  the host genome as CRISPRs.
- CRISPRs are transcribed and processed into an RNA sequence that binds and directs
  the nuclease Cas9 to a sequences (e.g., a phage), leading to its cleavage and the
  destruction of the phage.
- Gene editing repurposes this process by using artificial guide RNAs (gRNAs) that bind Cas9 and are complementary to a DNA sequence of interest.
- Once directed to the target sequence by the gRNA, Cas9 induces double-strand DNA breaks.
- Repair of the resulting highly specific cleavage sites can lead to somewhat random disruptive mutations in the targeted sequences (through nonhomologous end joining [NHEJ]), or the precise introduction of new sequences of interest (by homologous recombination).
- Both the gRNAs and the Case enzyme can be delivered to cells with a single easy-to-build plasmid. Which is substantiallybetter than other previous editing systems, cancers and other diseases, and rapidly generating transgenic animals from edited embryonic stem cells.
- On the flip side, it now is feasible to selectively "correct" mutations that cause hereditable disease, or perhaps more worrisome to just eliminate less "desirable"

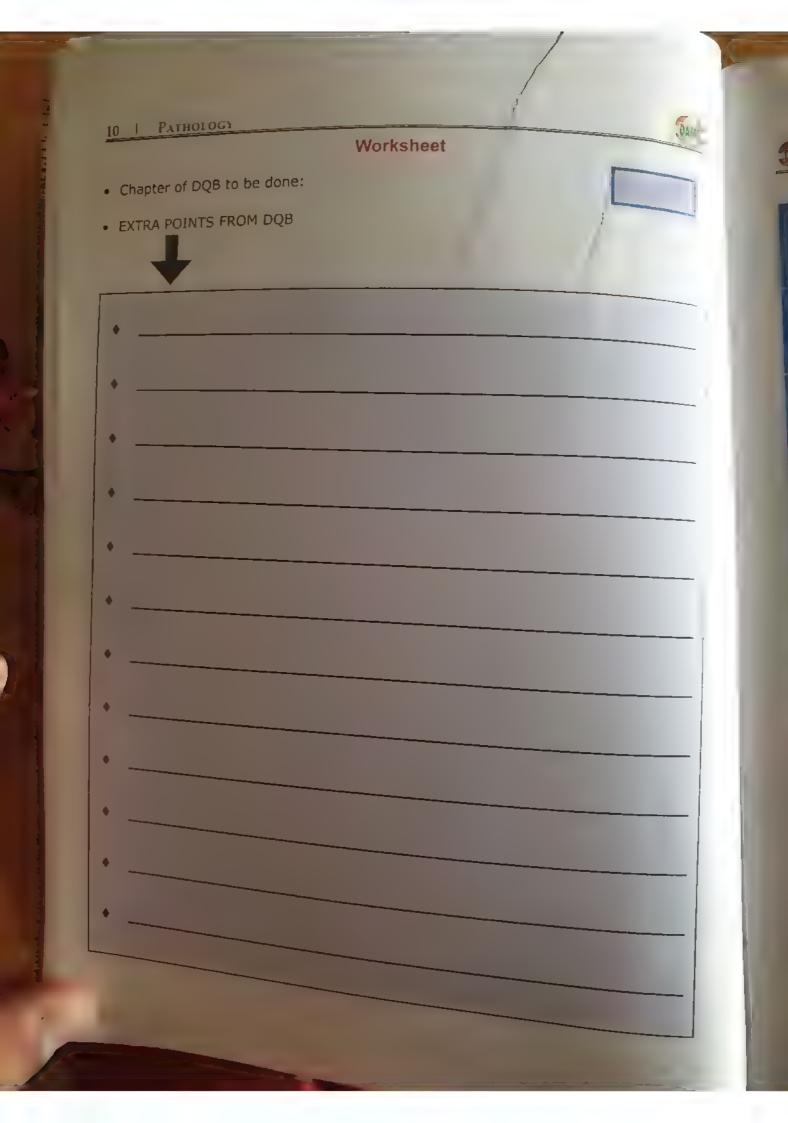




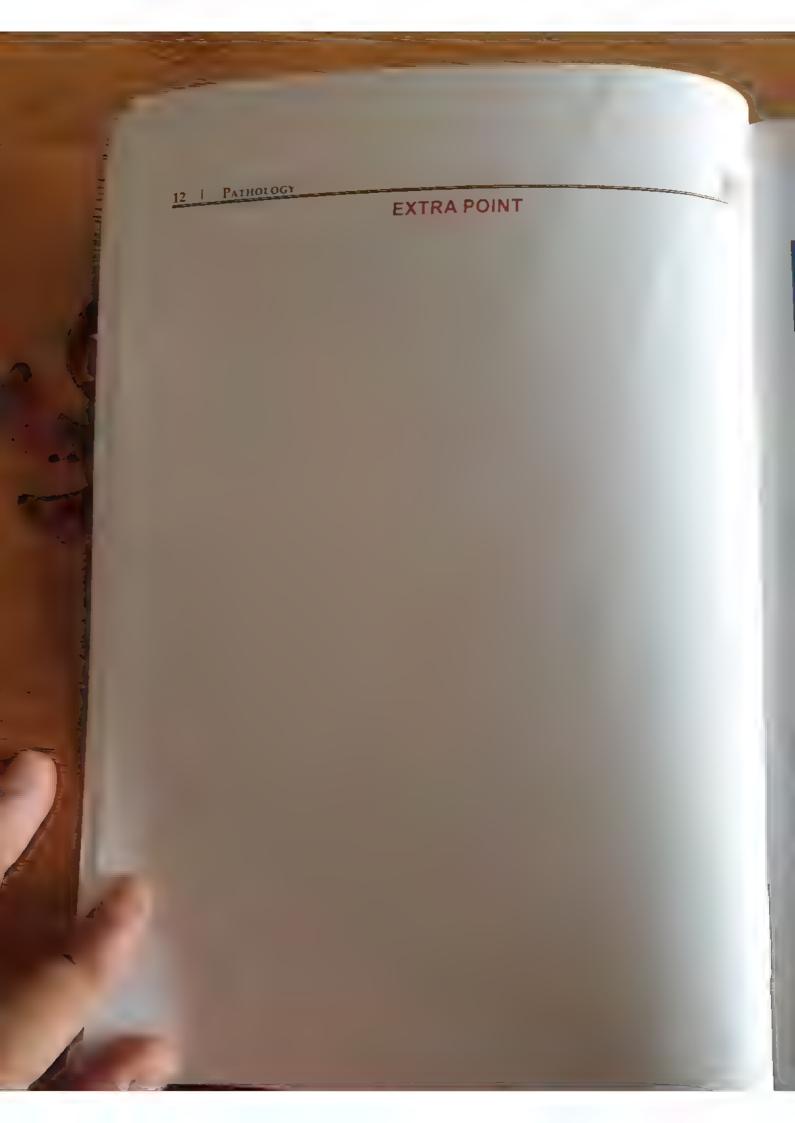
DNA with random mutation

DNA with specific mutation

Fig. 1.4











# CELLULAR ADAPTATIONS, INJURY AND DEATH

# CONCEPTS

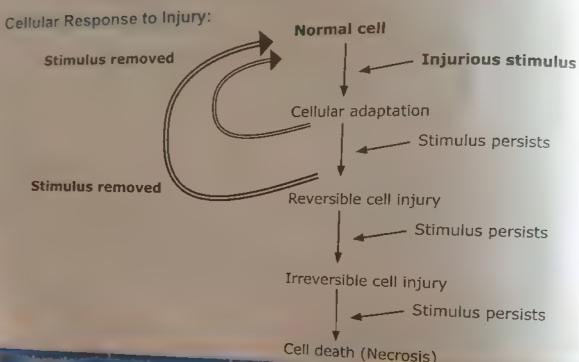
Concept 2.1. Cellular Changes During Injury

### PATHOLOGY

Concept 2.1: Cellular Changes During Injury Concept 2.1: Central Office with examples of cell adaptations, injury and LEARNING OBJECTIVE: Mechanisms with examples of cell adaptations, injury and death. Ceiluiar accumulations, Calcification, Ageing.

### Time Needed

30 mins 2 reading



<b>Chilejmoles</b>	The state of the s	Cell death (Necrosis)			
Hapatrophs	Increase in size of cells due increase in cellular contents () rganeiles)	Induced by mechanical sensation, growth factors and vasoactive agents.	Phosphoinositide 3 kinase Akt pathway (physiological and Signaling downstream of		
Hyperp 1814	Increase in number of cells	Physiological- compensatory	G protein coupled receptors (pathological).		
Atrophy	Decrease in size	hormones or growth factors	No genetic mutations like in Neoplasia, characteristic response to some viral intections like HPV		
Metalic a	Research change	and decreased protein ( and vay)	Causes DIPMED (mnemonie)*		
	of wach me idad cel type tepatrol il or mese of small is replaced by at other adult cel type	Due to repregramming of stem ceals that exist an normal tissue or of undifferentiated mesenchymal cells in connective tissue.	Columnar to Squamous- MOST COMMON- occurs in respiratory epithelium in response to smoke-		

10ST COMMON-occurs in respiratory epithelium in response to smoking and Vitamin A deficiency. Squamous to Columnar- in Barren's esophagus in response to acid reflux



and cell

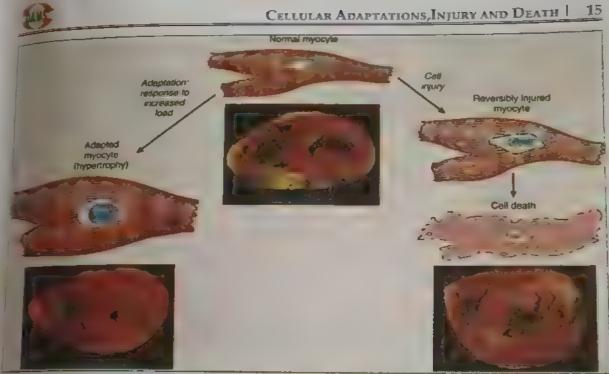


Fig. 2.1



Fig. 2.2

Physiological hypertrophy of uterus during pregnancy:

- A. Gross appearance of a normal uterus and a gravid uterus.
- B. Small spindle shaped uterine smooth muscle from a normal uterus.
- C. Large plump cells from a gravid uterus.

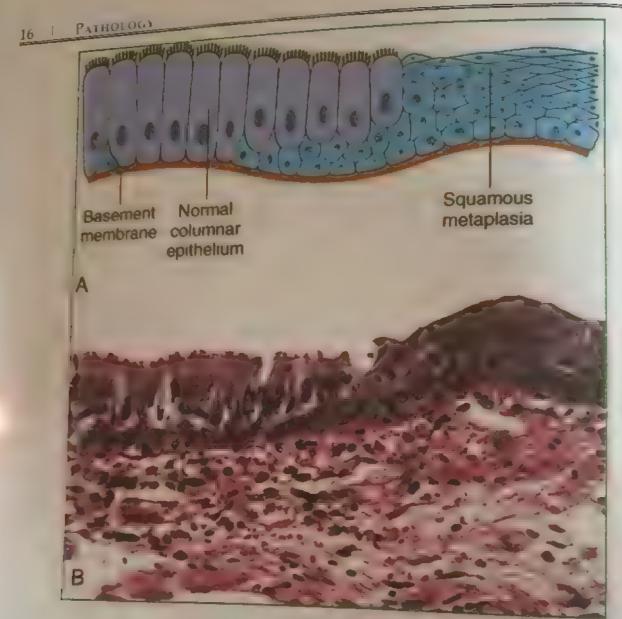


Fig. 2.3

# Metaplasia of columnar to squamous epithelium:

- A. Schematic diagram.
- B. Metaplasia of columnar epithelium (left) to squamous epithelium (right) in

L'implementation of the section	(right)
	Direction
Hypertrophy (dominant) + hyperplasia	Hyperplasia (dominant) + hypertrophy  Hyperplasia (dominant) + hypertrophy
Involution	
Atrophy	Hypertrophy Atrophy
	hyperplasia Involution



# Cellular Response to Injury Depends on:

- a. Type of injury.
- puration of injury.
- Type of cell injury.
- Cell's metabolic state.
- Cell's ability to adapt.

## Intracellular systems vulnerable to injury:

- a Cel membrane.
- Production of ATP via Aerobic respiration in mitochondria.
- Protein synthesis by Endoplasmic reticulum & Ribosomes.
- DNA in nucleus.

### Timescale of Reversible and Irreversible Injury:

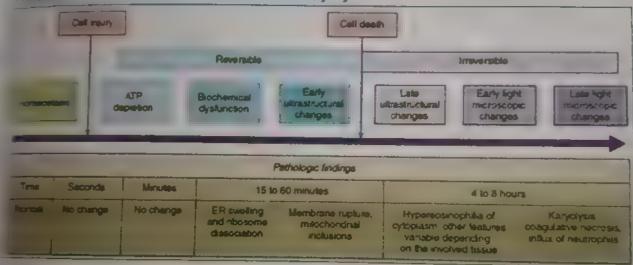


Fig. 2.4

### Important mechanisms of cell injury

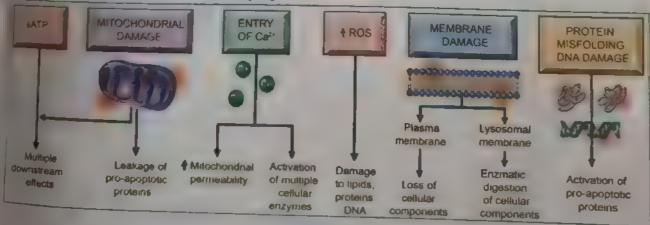


Fig 25

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i. Free radical injury

II. ATP depletion- seen in hypoxic cell injury in Acr depletor.

in Influx of calcium: Important mediator of cell injury especially in ischemic and tox.c

Second messenger

 Normal free cytosolic Ca- low conc. Intracellular calcium is sequestered in mitochondria and ER.

 Ischemic and toxins - increases cytosolic Ca due to influx of extra cellular Ca and release of Ca from mitochondria and ER.

Increase cytosolic Ca activates wide spectrum of enzymes.

Proteases - protein break down

ATP ases - ATP depletion

Phospholipids - cell membrane injury

Endonucleases - DNA damage.

iv. Increased cell membrane permeability.

Seen in most forms of cell injury

Biochemical mechanisms that contribute to membrane damage.

Mitochondrial dysfunction →↓ phospholipids synthesis.

 cytosolic Ca associated with ATP depletion → activation of phospholipases depletion of phospholipids from all membranes

Reactive oxygen species -> lipid per oxidation of membranes.

 Lipid breakdown products that accumulate in injured cell like unesterified FFA, acya Carnitine and lyso phospholipids have detergent effect on membranes and cause changes in membrane permeability.

v. Mitochondrial dysfunction – Targets for virtually all types of injurious stimuli

Decrease oxidative phosphorylation

Formation of mitochondrial permeability transition (MPT) channels.

Release of cyto chrome c, a trigger for apoptosis.

Mechanism of cell injury: Reversible cell injury

a. Decreased synthesis of ATP by oxidative phosphorylation

b. Decreased function of Na+K+ATPase membrane pumps

I. Influx of Na+ and water

II. Efflux of K+

III. Cellular swelling ~ earliest morphological feature of cell injury

iv. Swelling of the endoplasmic reticulum- hydropic change (degeneration) - vacuoles in c. Switch to glycolysis

I. Depletion of cytoplasmic glycogen

II. Increased lactic acid production

III. Decreased intra cellular pH

d. Decreased protein synthesis

i. Detachment of Ribosomes form the rough endoplasmic reticulum e. Plasma – membrane blebs and myelin figures may be seen

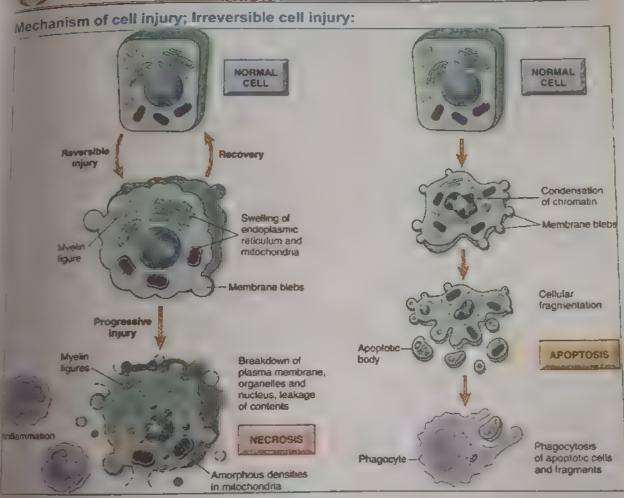


Fig. 2.6

- a. Severe membrane damage.
  - I. Membrane damage plays a critical role in irreversible injury.
  - II. Massive influx of calcium.
  - III. Efflux of intracellular enzymes and proteins into the circulation.

b. Marked mitochondrial dysfunction

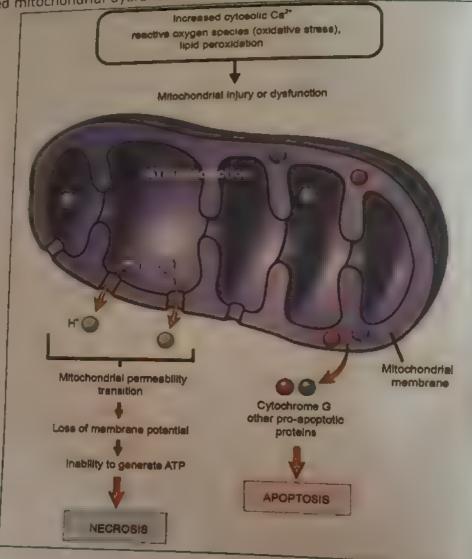


Fig. 2.7

- I. Mitochondrial swelling.
- II. Large flocculent densities are seen within the mitochondrial matrix (small densities can be seen in reversible injury also).
- III. Irreparable damage of the oxidative phosphorylation pathway.
- IV. Inability to produce ATP.
- c. Rupture of the lysosomes.
  - I. Release of lysosomal digestive enzymes into the cytosol.
- II. Activation of acid hydrolases followed by autolysis.
- d. Nuclear changes.
- Pyknosis: degeneration and condensation of nuclear chromatin.
- II. Karyorrhexis: nuclear fragmentation.
- III. Karyolysis: dissolution of the nucleus



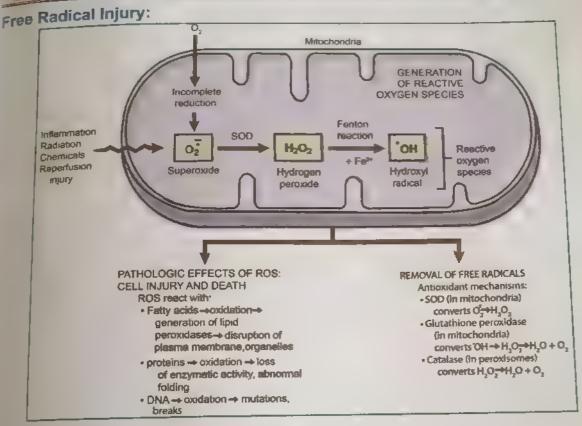


Fig. 2.8

- a. Definition: Molecules with unpaired electrons in the outer orbit.
  - I. Extremely reactive, enter into reactions with lipids, proteins, carbohydrates.
  - II. Associated with oxygen, carbon, nitrogen.
  - III. Oxygen associated are: Super oxide, hydroxyl. Hydrogen peroxide.
- IV. Carbon associated are: CCL,

V. Nitrogen associated are: NO <sub>2</sub>			
Reactive Oxygen Species (ROS)			
Molecule	Attributes		
Hydrogen peroxide (H, O,)	Forms free radicals via Fe <sup>2+</sup> - catalyzed Fenton reaction Diffuses widely within the cell		
Superoxide anion (O <sub>2</sub> -)	Generated by leaks in the electron transport chain and some cytosolic reactions Produces other ROS Does not readily diffuse far from its origin		
Hydroxyl radical (OH•)	Generated from H <sub>2</sub> O <sub>2</sub> by Fe <sup>2+</sup> -catalyzed Fenton reaction  The intracellular radical most responsible for attack on macromolecules (Most potent radical (*)		
Peroxynitrite (ONOO•)	Formed from the reaction of nitric oxide (NO) with O, - Damages macromolecules		
Lipid peroxide radicals (RCOO+)	Organic radicals produced during lipid peroxidation		
Hypochlorous acid (HOCI)	Produced by macrophages and neutrophils during respiratory burst that accompanies phagocytosis Dissociates to yield hypochlorite radical (OCI-)		

### PATHOLOGY

# b. Mechanism of free radical damage

- I. Lipid peroxidation of membranes
- II. Oxidative damage to proteins.

III. DNA breaks

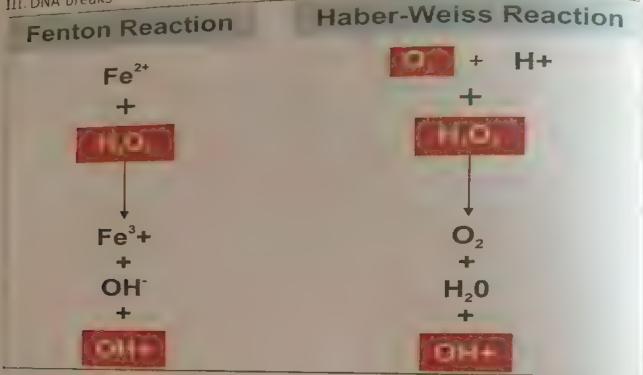


Fig. 2.9 Fenton and Haber-Weiss reactions to generate the highly reactive hydroxyl radical. Reactive species are shown in red. Fe2+ = ferrous iron; Fe3+ = Ferric iron, H+ = hydrogen ion, H2O2 = hydrogen peroxide. OH- = hydroxide; OH. = hydroxyl radical

## c. Inactivation of free radicals in the body

- Antioxidants: Vit A&C. Sulpha containing compounds like cysteine & Glutathione
- II Serum proteins: Albumin, Ceruloplasmin, Transferrin
- III. Enzymes: superoxide Dismutase, Catalase, Glutathione Peroxidase

# Free radicals can cause cell injury and death by necrosis as well as apoptosis.

### Cell Death:

Necrosis

Morphological types of necrosis

# a. Coagulative Necrosis

- I. Most common form of necrosis.
- II. Due to denaturation and coagulation of proteins in the cytoplasm. III. Micro: Loss of nucleus but cellular outline is preserved.
- IV. Common in infarct of solid organs like Hear, Liver, Kidney, limb (dry gangrene)



Coagulative necrosis. A, A wedge-shaped kidney infarct (yellow). B, Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate (which is difficult to discern at this magnification).

### b. Liquefactive necrosis

- 1. Cellular destruction by hydrolytic enzymes.
- II. Due to autolysis and heterolysis
- III. Occurs in abscesses, brain infarct, pancreatic necrosis and wet gangrene.

#### c. Caseous necrosis

- I. Combination of liquefactive and coagulative necrosis
- II. Gross-friable, soft, and cottage cheese like appearance
- III. Characteristic of tuberculosis

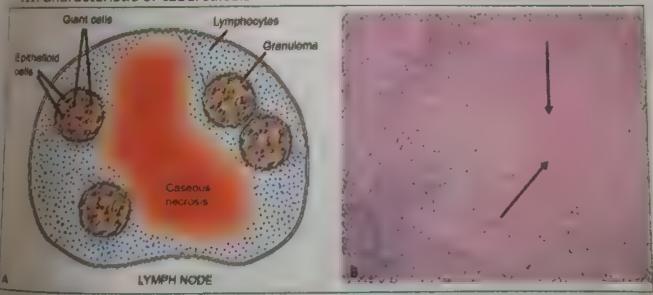


Fig. 2 11. Caseous necrosis in a tuberculous lymph node (A), the typical amorphous, granular, eosinophilic, necrotic center is surrounded by granulomatous inflammation (B) Photomicrograph showing a tuberculosis granuloma with central caseous necrosis (arrows).

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### d. Fat necrosis

- I. Caused by action of lipases on fatty tissue
- II. Grossly: Chalky white in appearance
- III. Seen in breast and pancreatitis.

### e. Fibrinoid Necrosis

- I. Necrotic tissue that histologically resembles fibrin
- II. Micro: Has an eosinophilic (pink) homogenous appearance III. Seen in malignant hypertension, type II and III hypersensitivity reactions, vascu
- hyper acute and acute humoral graft rejections



Fig. 2.12

Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei). f. Gangrenous necrosis:

- I. Gross term used to describe dead tissue.
- II. Common sites: Lower limbs, Gl tract, testes.
- III. Dry gangrene: microscopic pattern is coagulative necrosis.
- IV. Wet gangrene: microscopic pattern is liquefactive necrosis.

## Necrosis morphology

- 1. Increased eosinophilia
- 2. Myelin figures
- 3. Nuclear changes (karyolysis, pyknosis, karyorrhexis) **Apoptosis**

- a. Specialized form of programmed cell death.
- b. Apoptosis is and active process regulated by genes and involves RNA and Protein
- c. Often affects only single cells or small groups of cells.



# Physiological Apoptosis:

During Embryogenesis- Implantation, Organogenesis, Developmental Involution, and Metamorphosis (\*).

. Involution of hormone dependent tissues upon hormone withdrawal (endometrium after menstrual cycle, ovarian follicles after menopause, breast after weaning and prostrate after castration).

Cell loss in proliferating cell populations like immature lymphocytes in bone marrow and thymus which fail to express useful antigen receptors.

Elimination of potentially harmful self-reactive lymphocytes.

. Death of host cells which have completed their function (such as neutrophils in acute inflammatory response).

## Pathological Apoptosis:

DNA damage.

- Accumulation of misfolded proteins in ER leads to a condition called ER stress.
- Cell death in certain infections (viral mostly) and transplant rejection and tumours
- Pathological atrophy.

### Morphological Appearance:

- I. Cell shrinks in size with tight packing of organelles.
- II. Nuclear chromatin condensation.
- III. Formation of cytoplasmic membrane blebs.
- IV. Break down of the cell into fragments or apoptotic bodies.
- V. Phagocytosis of apoptotic bodies by macrophages.
- VI. A lack of inflammatory response.

### Stimulus for Apoptosis:

- DNA damage by radiation toxins and free radicals stimulates p53.
- II. Lack of hormones, cytokines, or growth factors start the intrinsic pathway (mitochondrial pathway) of apoptosis.
- III. Receptor ligand signals start the extrinsic (death receptor initiated pathway).

Fas binding to the Fas ligand. Tumor necrosis factor binding to TNF Receptor1.

Agarose gel electrophoresis of DNA extracted from culture cells. Ethidium bromide stain; photographed under ultraviolet illumination. Lane A, Viable cells in culture. Lane B, Culture of cells exposed to heat showing extensive apoptosis; note ladder pattern of DNA fragments, which represent multiples of oligonucleosomes. Lane C, Culture showing cell necrosis; note diffuse smearing of DNA



Fig. 2.13

#### Apoptosis is regulated by genes:

- I. Bci-2 family regulates apoptosis. Bcl-2 and bcl-X reside in the inner mitochondrial membrane and they inhibit apoptosis. Bak, Bax, and Bim stimulate apoptosis. When cell does not get hormones or growth factors, bcl-2 and bcl-X are replaced by Bax, bak and Bim. They increase the permeability of mitochondrial membrane which results in leakage of cytochrome c of respiratory chain. This blinds Apaf-1 (Apoptosis activating factor -1). Which in turn activates caspases.
- Anti-apoptotic proteins are Bcl-2, Bcl-x, and Mcl-1.
- Sensors are also members of the Bcl family, and they include proteins called Bim, Bid, and Bad and are also called as "BH3-only proteins." They activate two critical (pro-apoptotic) effectors, Bax and Bak, which form oligomers that insert into the mitochondrial membrane and create channels that cytoplasm.
- Extrinsic and intrinsic pathways for initiating apoptosis are distinct because
  they involve fundamentally different molecules for their initiation, but there
  may be interconnections between them. For instance, in hepatocytes and
  several other cell types, Fas signaling activates a BH3-only protein called
  Bid, which then activates the mitochondrial pathway.

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apoptotic		Antionautotic
Antiapoptotic Proteins	Displace Bax and Bak	Antiapoptotic
	Bad	Bcl-2
	Bid	Bel X
	Bık	Bel-X
	Nox	A1
	Puma	Ku70
7 3 7 6	Noxa	Mcl-1

[] P-53(stimulates apoptosis): Elevated by DNA injury and arrests the cell in  $G_1$  phase of cell cycle. If DNA repair is impossible. p-53 stimulates apoptosis.

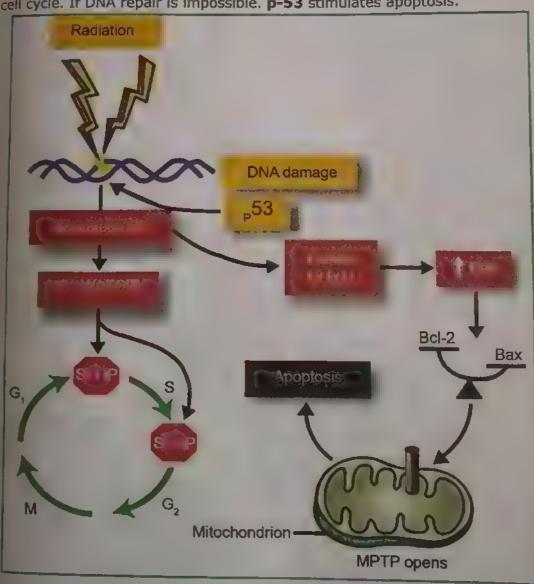


Fig. 2.14

Fig. 2.15

Membrane bleb

Apoptotic body

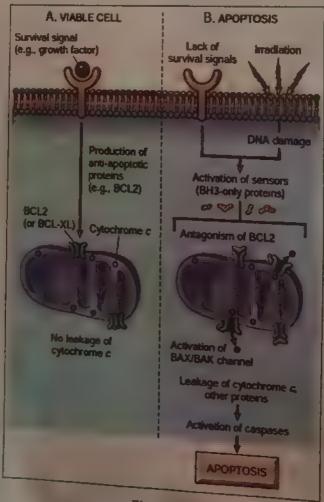


Fig. 2.16



The intrinsic (mitochondrial) pathway of apoptosis. A, Cell viability is maintained by the induction of anti-apoptotic proteins such as Bcl-2 by survival signals. These proteins maintain the integrity of mitochondrial membranes and prevent leakage of mitochondrial proteins. B, Loss of survival signals, DNA damage, and other insults activate sensors that antagonize the anti-apoptotic proteins and activate the pro-apoptotic proteins Bax and Bak, which form channels in the mitochondrial membrane. The subsequent leakage of cytochrome c (and other proteins, not shown) leads to caspase activation and apoptosis

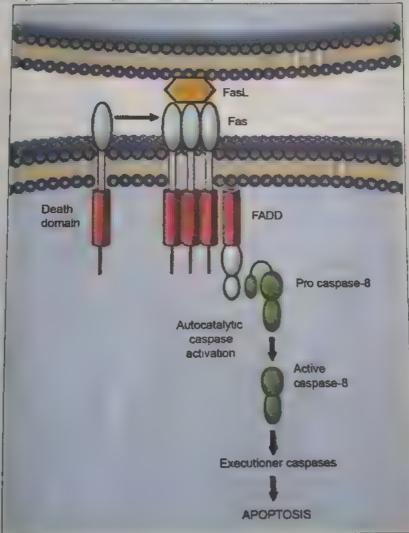


Fig. 2.17

The extrinsic (death receptor-initiated) pathway of apoptosis, illustrated by the events following Fas engagement. FAAD, Fas-associated death domain; FasL, Fas ligand.

# Features of Necrosis and Apoptosis

	The state of the s	The state of the s
	Emarged (swelling)	Reduced (shrinkage)
Cell size	Pyknosis * karyorthevis *	Fragmentation into nucleosome size fragments &
Nucleus	katyolysis	condensation of chromatin
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cedular contents	Enzymatic digestion, may leak out of cell	Intact; may be released in apoptotic bodies
Adiacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

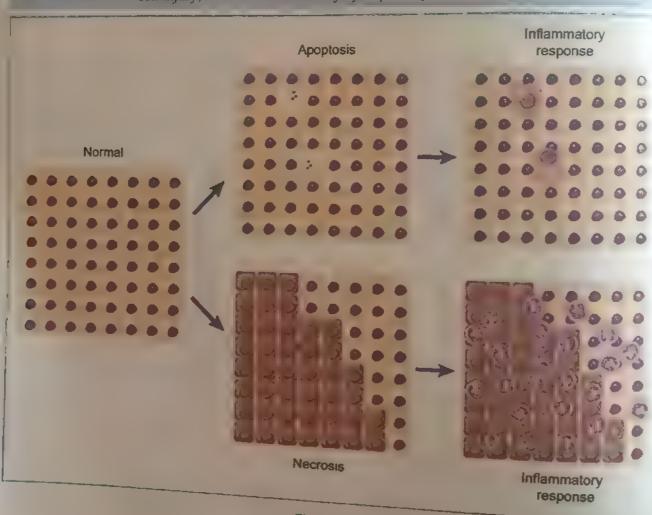


Fig. 2.18



# f. Execution of apoptosis:

I. Mediated by Caspases.

II. Caspases digest nuclear and cytoplasmic proteins.

III. Caspases also activate endonucleases.

# g. Examples of apoptosis:

Embryogenesis: organogenesis and development.

II. Hormone dependent Apoptosis e.g. menstrual cycle.

III. Thymus: selective death of lymphocytes.

IV. V ral diseases: Viral hepatitis (Councilman Bodies).

v. Cystic fibrosis: duct obstruction and pancreatic atrophy.

# NECROPTOSIS (Robbins 9th edition- NEW TOPIC)

As the name indicates this form of cell death is a hybrid that shares aspects of both necrosis and apoptosis.

In sharp contrast to apoptosis, the genetic program that drives necroptosis does not result in caspase activation and hence it is also known as "caspase independent" programmed cell death

### **Necroptosis and Pyroptosis**

- Necroptosis resembles necrosis morphologically and apoptosis mechanistically as a form of programmed cell death.
- Necroptosis is triggered by ligation of TNFR1, and viral proteins of RNA and DNA viruses.
- Necroptosis is caspase-independent but dependent on signaling by the RIP1 and RIP3 complex.
- RIP1-RIP3 signaling reduces mitochondrial ATP generation, causes production of ROS, and permeabilizes lysosomal membranes, thereby causing cellular swelling and membrane damage as occurs in necrosis.
- Release of cellular contents evokes an inflammatory reaction as in necrosis.
- Pyroptosis occurs in cells infected by microbes.lt involves activation of caspase-1
   which cleaves the precursor form of IL-1 to generate biologically active IL-1. Caspase-1
   along with closely related caspase-11 also cause death of the infected cell.

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Fig. 2.19

CELL DEATH BY APOPTOSIS

CELL DEATH BY NECROPTOSIS

Molecular mechanism of TNF mediated necroptosis. Cross linking TNFR1 by TNF causes recruitment of RIP 1 and RIP 3 along with caspase 8. Activation of caspase leads to and RIP 3 to initiate signals that affect mitochondrial generation of ATP and ROS. This is



cells.

protein

tion of

otor

pefect in intracellular transport and secretion of critical proteins.

a IAT deficiency - Mutations in protein slow the folding, partially folded protein accumulates in ER of Liver and is not secreted - Emphysema.

Cystic fibrosis

Familial hyper cholesterolemia

p. ER stress induced by misfolded / unfolded protein. Misfolded protein in ER -> Unfolded protein response.

unfolded Protein response

Initially cytoprotective - increase chaperones and decrease protein translation

Later, activates caspases 12 in ER- Cell death by apoptosis

E.g. Neurodegenerative diseases- Alzheimer's disease, Huntington, Parkinson's disease? Type II Diabetes

### **Exogenous pigments**

Anthracotic pigment of lung is secondary to inhalation of carbon

II. Tattoos cinnabar, India ink dyes used

### **Endogenous pigments**

. Lipofuscin:

Wear and tear pigment tell tail sign of free radical injury; peri nuclear

Yellow brown pigment; indigestible material within lysosomes common in liver and heart Brown atrophy; atrophy of organ with lipofuscin pigment.

Melanin: Brown black pigment found in melanocytes and substantia nigra

Hemosiderin: Golden yellow brown pigment found in areas of hemorrhage / bruises systemic iron overload Prussian blue positive - Perl's reaction

#### Hyaline change:

Nonspecific term used to describe any intracellular or extra cellular alteration that has pink homogenous appearance on H and E

i. E.g. of intracellular hyaline Resorption droplets in proximal tubules of kidney Russel bodies Alcoholic hyaline

II. E.g. of extra cellular hyaline Hyaline arterioles clerosis Amyloid Hyaline membrane disease of new born

### Pathological calcification

### A Dystrophic calcification:

- 1. Precipitation of calcium phosphate in dying or necrotic tissue
- II. S. calcium levels is normal with normal calcium metabolism
- iii. Examples: calcification in areas of fat necrosis, calcification in areas of coagulative and caseous necrosis; psammoma bodies- laminated concretions that occur in meningiomas, papillary carcinoma of thyroid and ovary; Monckebergs medial calcific stenosis and atherosclerotic plaques

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- i. Protein accumulates in proximal renal tubules in proteinuria ii. Russell bodies: intracytoplasmic accumulation of immunoglobulins in plasma cells.
- in. Defective protein folding can also result in protein accumulation.

# Normal Protein Synthesis and folding Proteins synthesized as polypeptide chains on ribosomes.

- $\bullet$  Chains arranged into  $\alpha$  helices /  $\beta$  sheets and folded properly.
- Protein folding and transportation across E.R., Golgi and beyond is aided by protein c. a chaperones.
- Chaperones:
- Synthesized constitutively, affect normal intracellular protein trafficking
- Induced by stress and heat shock proteins e.g. hsp 70, hsp 90.
- 'Rescue' shock stressed proteins from misfolding.
- If folding is not successful, ubiquitin (a type of chaperones) facilitate degradation of

damaged proteins.				
Commission of Biquitin-Protessome System December 19				
Disease	Lbiquitin-Proteasome System Activity	Anatomic Effect		
Neurologic Diseases (Diseases Associated With Neuron Loss)				
Parkinson disease	Decreased	Lewy bodies		
Alzl.eimer disease	Decreased	Amyloid plaques, neurofibrillary tangles		
Amy otrophic lateral sclerosis	Decreased	Superoxide dismutase aggregates in motor neurons		
Huntington disease	Decreased	Polyglutamine inclusions		
Autoimmune Diseases		TO STANDARD		
Sjogren syndrome	Decreased	Chronic inflammation		
Metabolic Diseases		The intermitation		
Type II diabetes mellitus	Increased	Insulin insensitivity		
Cataract formation	Decreased			
Muscle Wasting		Aggregated oxidized proteins		
Aging	Increased			
Cancer and other chronic disease	Increased	Atrophy		
Cardiovascular				
Ischemia/repetfusion	Decreased			
Pressure overload	Decreased	Myocyte apoptosis		
		Myocyte apoptosis		

# PYROPTOSIS (Robbins 9th edition- NEW TOPIC)

Another form of programmed cell death

Accompanied by release of fever inducing cytokine IL1 and because it bears some biochemical similarities with apoptosis

Microbial products enter cytoplasm à cytoplasmic immune receptors recognize them  $\rightarrow$  activate the multiprotein complex called INFLAMMASOME  $\rightarrow$  activates caspase 1  $\rightarrow$ cleaves a precursor form of IL 1

Unlike classical apoptosis, this pathway is characterized by swelling of cells, loss of plasma membrane integrity and release of inflammatory mediators.

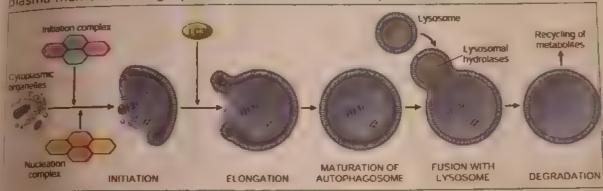


Fig. 2.20

#### Intracellular accumulation:

#### Lipids:

- i. Triglycerides (e.g. Fatty change in liver cells)
- ii. Cholesterol (e.g. Atherosclerosis, xanthomas)
- iii. Complex lipids (e.g. Sphingolipids accumulation of immunoglobulins in carbon dust)

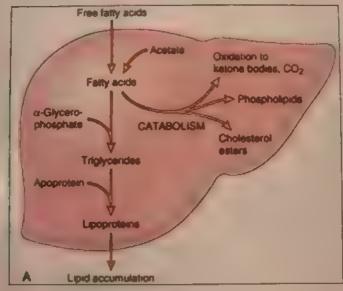


Fig. 2.21

# B. Metastatic calcification:

- i. Precipitation of calcium phosphate in normal tissues due to hypercalcemia
- ii. Causes: Hyper parathyroidism

Parathyroid adenomas

Renal failure

Paraneoplastic syndrome

- Vitamin D intoxication

Milk-alkalı syndrome

Sarcoidosis

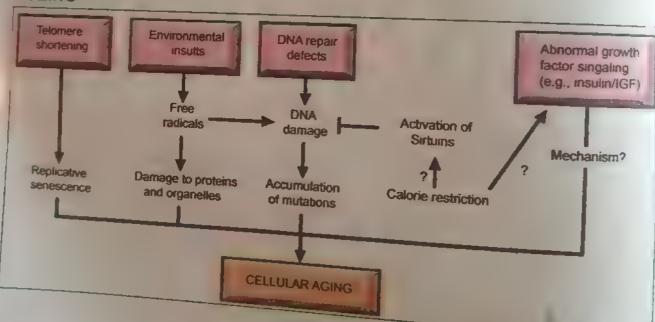
Paget's disease

Multiple myeloma

Meta static cancer to the bone

- III. Location of calcification: Begins in mitochondria in all the organs except kidne. where it begins in the basement membrane of the tubules.
- iv. Stains used for demonstration of calcium: Von Kossa & Alizarin Red -S
- v. Metastatic calcification occurs widely throughout the body but principally affects the interstitial tissues of the gastric mucosa, kidneys, lungs, systemic arteries and pulmonary veins.

#### **AGEING**



Mechanisms of cellular aging. Genetic factors and environmental insults combine to produce the cellular abnormalities characteristic of aging. How calorie restrictions prolong life span is net established. IGF, insulin-like growth

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affects ries and

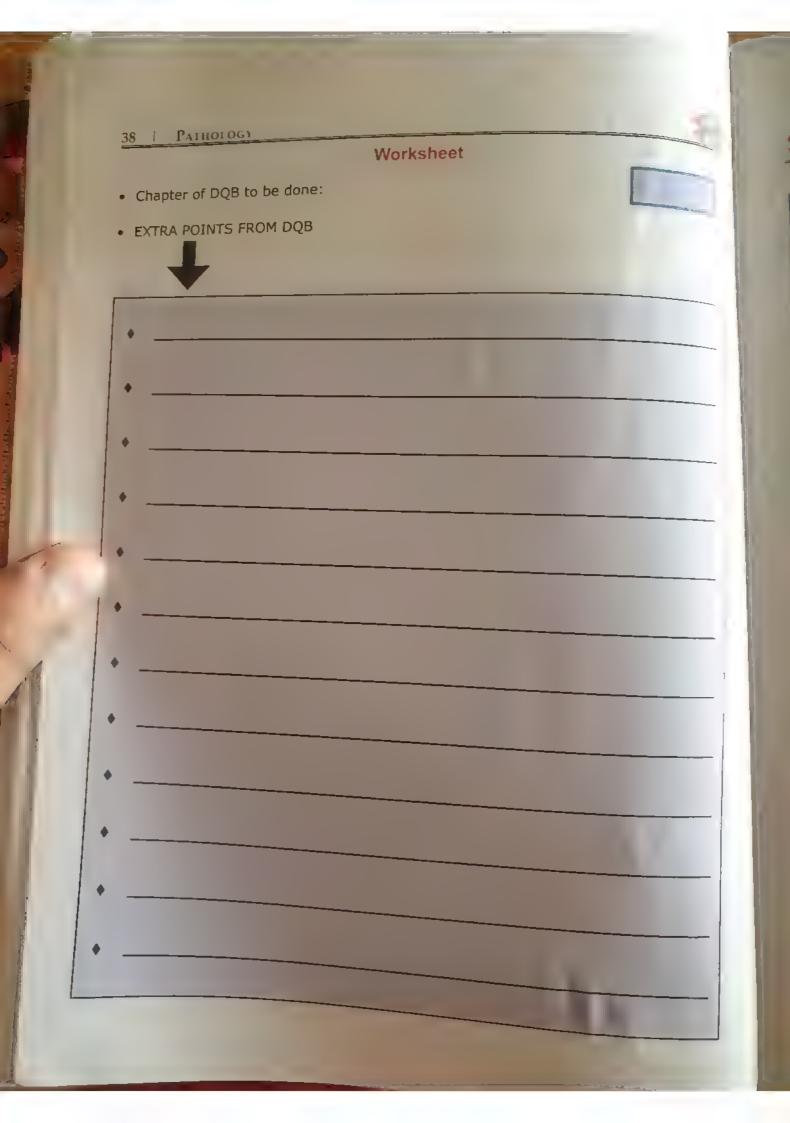
GF)

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Superimental Factors	That believes Biological to glog (*)
factors That Increase Longevity	Factors That Decrease Longevity
Victations in p53, p14 kg, p16 skii, etc	Increased p53 activation
Decreased metabolic rate	Increased metabolic rate
Calone restriction	Increased oxidative stress
lacreased Sirt 1	Increased mTOR activity
Age mutations	Increased cell cycle control proteins
reased antioxidant defenses	Genetic factors
pisodic stress	
in Chatars	

Celiular ageing results from a combination of accumulating cellular damage, reduced capacity to divide, reduced ability to repair damaged DNA and defective protein homeostasis.

- 1. Accumulation of DNA damage: defective DNA repair mechanisms; conversely, caloric restriction activates DNA repair and is known to prolong ageing in model organisms
- 2. Replicative senescence: reduced capacity of cells to divide secondary to progressive shortening of chromosomal ends (telomeres)
- 3. Defective protein homeostasis: resulting from defective proteasome and chaperone functions
- 4. Nutrient sensing system: caloric restriction inreases longevity. Mediators may be reduced IGF-1 signalling and increase in sirtuins





### **Active Recall**





# Inflammation and Wound Healing

# CONCEPTS

concept 3.1. Inflammation and Wound Healing



# Concept 3.1: Inflammation and Wound Healing Time Needed

I" reading 2 " reading

### Inflammation:

Response of vascularized connective tissue to injury.

Fundamentally protective response, may be potentially harmful.

#### Acute:

Rapid onset (sec. – min) short duration: lasts for min → hrs. → day.

Features exudation of fluid & PP (oedema) extravasation of leukocytes ( Neutrophils)

#### Chronic:

- Longer duration.
- Associated with presence of lymphocytes & macrophages.
- · Prolif. Of BVS, fibrosis, tissue necrosis.

#### Celsus

(3000 B.C.)- Rubor, Tumor, Color, Dolor, Virchow- Functio Iaesa. Elie Metchnikoff → Phagocytosis. Sir Thomas Lewis → Histamine.

#### Acute Inflammation:

#### Events:

### Vascular Events:

#### Cellular Events:

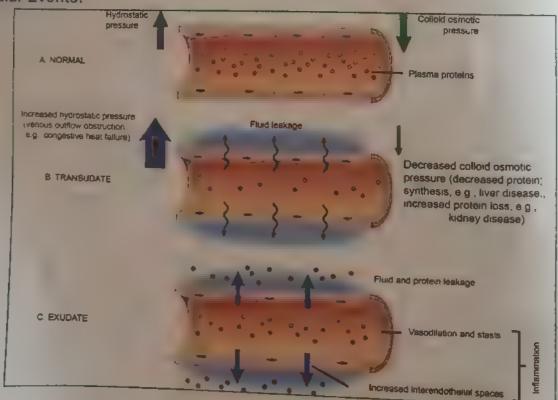


Fig. 3.1

DANS

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Exudate	Transudate
Inflamm. Oedema	N.inflamm.
î Permeability	Hydrostatic.
	Imbalance
Escape of fluids	Ultra – filtrate
	of plasma
Proteins, cells	↓ / No proteins
	(albumin)
Sp. Gravity > 1.020	< 1.012

Formation of transudates and exudates. A, Normal hydrostatic pressure (blue arrows) is about 32 mm Hg at the arterial end of a capillary bed and 12 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg (green arrows), which is equal to the mean capillary pressure. Therefore, the net flow of fluid across the vascular bed is almost nil. B, A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure. C, An exudate is formed in inflammation, because vascular permeability increases as a result of increased interendothelial spaces.

#### Pus:

Purulent Exudate

#### Stimuli for acute inflammation:

- Infections (bacterial, viral, parasitic) and microbial toxins.
- Trauma ( blunt, penetrating ).
- Physical and chemical agents (thermal injury, radiation, chemicals).
- Tissue necrosis.
- Foreign bodies ( splinters, dirt, sutures ).
- · Immune reactions.

### The steps of inflammatory response can be remembered as the five Rs-

- 1. Recognition of the injurious agent.
- 2 Recruitment of leucocytes.
- 3. Removal of the agent.
- 4. Regulation (control) of the response.
- 5. Resolution (repair).

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Fig. 3.2

Repair

### Vascular changes:

Vasodilation is one of the earliest manifestations of acute inflammation; vasodilation first involves the arterioles and then leads to opening of new of heat and redness (erythema) at the site of inflammation.

Vasodilation

Of arterioles -- opening of capillary beds

(† Blood flow, heat, redness)

Increased permeability of microvasculature: (Most characteristic feature of acute inflammation)

Out pouring of protein rich fluid (edema)

Concentration of cells in small vessels, 1 viscosity

Dilated BVs packed with Red Cells Stasis

▶ Leukocyte Margi nation

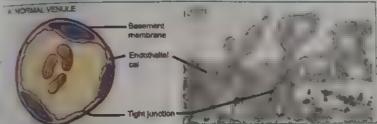
Peripheral orientations of leukocytes

(Transient sticking)

Rolling

Migration

### Mechanism of increased Vascular Permeability:





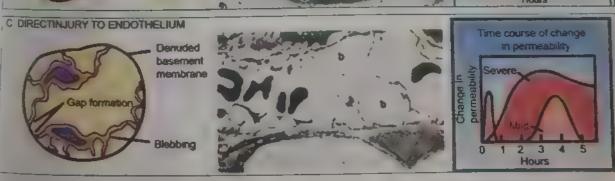


Fig. 3.3: Responses of the microvasculature to injury A. The wall of the normal venule is sealed by tight junctions between adjacent endothelial cells. B. During mild vasoactive mediator induced injury, the endothelial cells separate and permit the passage of the fluid constituents of the blood. C. With severe direct injury, the endothelial cells form blebs (b) and separation the underlying basement membrane. Areas of denuded basement membrane (arrows) allow a prolonged escape of fluid elements from the microvasculature.

### Cellular Events:

- i. Adhesion & Transmigration.
- ii. Chemo taxis.
- iii. Phagocytosis.

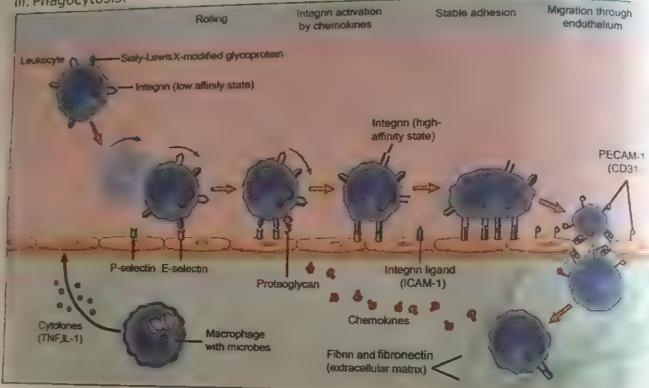


Fig. 3.4:

# 1. Adhesion & Transmigration:

### Steps:

- Lumen: Margination.
- Rolling transient adhesion.
- Transmigration across endothelium (diapedesis).
- Migration in interstitial tissue (to chemo tactic stimulus).

Stasis → Margi nation → Rolling

Firm adhesions (pebbles / marbles pavementing)

E/C Space ← Insert pseudopodía b/w endothelial cells

Adhesion and transmigration require:

- Complementary adhesion molecules binding.
- Chemical mediators.





# Adhesion Molecules:

- Selection E.Selectin, P.Selectin, L.Selectin.
- Immunoglobulins ICAM 1, VCAM-1.
- . Integrins Heterodimeric glycoproteins ( $\alpha$  &  $\beta$  chain).
  - . 32 integrin LFA-1, MAC-1 (binds ICAM-1).
  - » р 1 integrin VLA4 (binds VCAM-1).
- Mucin like Glycoproteins gly CAM-1.

, (psi.	I onkoyat Rwitpitti	( India living
. P selectin (on endothelium & platelets) (GMP 140 PADGEM)	Stalyl Lewis X PSGL-1 PSGL-1	• Rolling
E selection (CD 62 F ELAM 1) (on endothelium) [CAM-1]	Sally Lewis X β – integrins (CD 11/CD 18)	<ul> <li>Rolling</li> <li>Adhesion to activated endothelium</li> <li>Adhesion, arrest, transmigration</li> <li>Adhesion</li> </ul>
CAM-1  Giycam-1	(LFA-1, MAC-1) $\alpha_{4}\beta_{1}$ (VLA-4) $\alpha_{4}\beta_{5}$ (LPAM -1) L selectin (LAM-1)	Lymphocyte homing to high endoth. Venules
CD 31	CD 31	Leucocytes migration through endothelium



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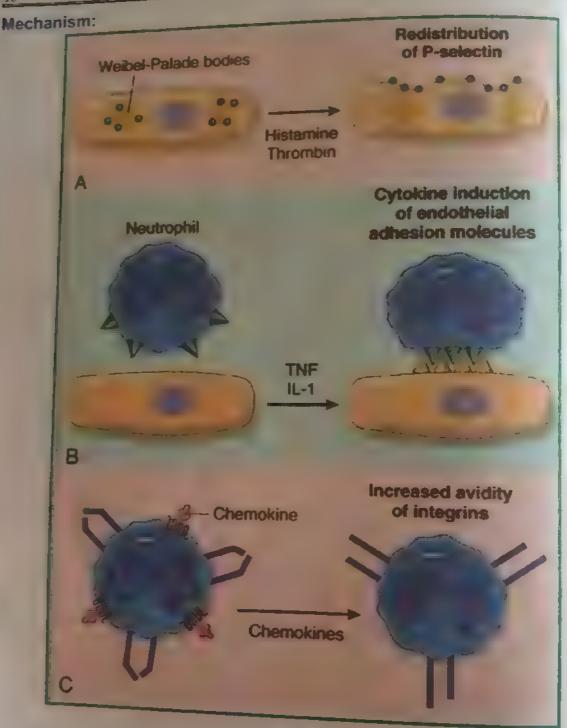


Fig. 3.5:

Regulation of expression of endothelial and leukocyte adhesion molecules. As creased surface expression of selectins and ligands for integrins upon cytokine by chemokines. Clustering of integrins contributes to their increased binding avidity (not shown). IL-1, interleukin-1; TNF, tumor necrosis factor.



# Impaired Leukocyte adhesion ->

Recurrent bacterial infection

Defect

L AD I: Absent β2 chain of LFA-1 & MAC-1 intergrins

L AD II: Absent sialyl lewis X- defect in fucose metabolism

# Transmigration (Predominantly venules):

• Intercellular jns - PECAM-1 / CD 31.

Pierce the basement membrane by? Secreting collagenases.

1. 6-24 hrs- Neutrophils.

24-48 hrs- Monocytes Because of

Induction / activation of different adhesion Molecules.

· Specific chemotactic factors in different Phase.

Neutrophils- short life (apoptosis after 24-28 hrs).

2. Pseudomonas: Neutrophils (2-4 days).

3. Viral infection Lymphocytes (First to arrive).

4. Hypersensitivity reactions: Eosinophils.

#### Chemotaxis:

locomotion oriented along a chemical gradient.

Chemo attractants Exogenous- bacterial products

Endogenous

 Complement comp. (C5a)

Product of lipooxygenase pathway  $(LTB_{4})$ 

Cytokines (IL8)

### **How Does A Leucocyte Move?**

Receptor (Seven transmembrane G protein coupled) - Ligand binding

Inactive GDP form converted to active GTP form

Phospholipase C activation (PLC-) and PI3K

Acts on membrane inositol phospholipids

Increased cytosolic, Ca and polymerization of actin at leading edge of cell. Actin regulating proteins- Filamin, Gelsolin, Profilin and Calmodulin also interact.

### PATHOLOGY

# Leukocytle Activation:

- Production of arachidonic acid metabolites.
  - · Activation of phospholipase A.
    - Degranulation & secretion of lysosomal enzymes & activation of oxidative burs
    - Secretion of cytokines which regulates inflammatory reaction.
    - Modulation of leukocyte adhesion molecules.
  - "Expression"

Increase adhesion of leucocytes to endothelium

- TAvidity
- Priming: \* rate & extent of leukocyte activation by mediator that itself causes little activation (e.g., TNF).
- Toll like receptors (TLRs) activate leucocytes in response to different types and components of microbes.
  - 10 TLRs identified till date
  - TLR- ligand binding → production of microbicidal substances and cytokines.
- Seven transmembrane 6 couples receptors.
  - Have 7 transmembrane a helical domain.
  - Ligands are-short acting peptides with N-Formyl methioyl residue, chemokines and lipid mediators - PAF, PGE, and LTB4.
  - Result in chemotaxis.
- Receptors for cytokines like IFN-GAMMA
  - Major macrophage activating cytokine.
- Promote phagocytosis.

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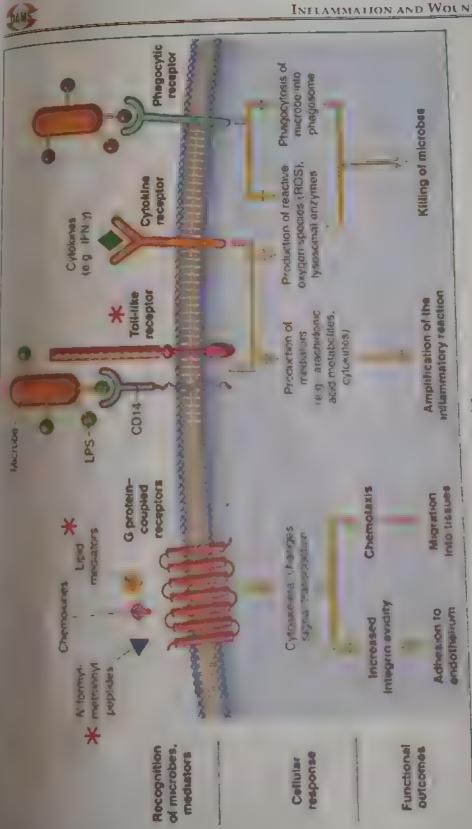


Fig 3.6:



### Phagocytosis: 3 Steps:

- 1. Recognition & attachment of particle to be ingested.
- 2. Engulfment- formation of phagocytic vacuole.
- 3. Killing or degradation.

### Recognition & attachments:

Leucocytes recognize microbes and dead cells by receptors.

- Mannose receptor- bind mannose and fucose residues of glycoprotein in microbial cel,
- Scavenger receptors- originally defined as molecules that bind modified LDL particles. Also bind microbes.
- Mac 1 integrins.

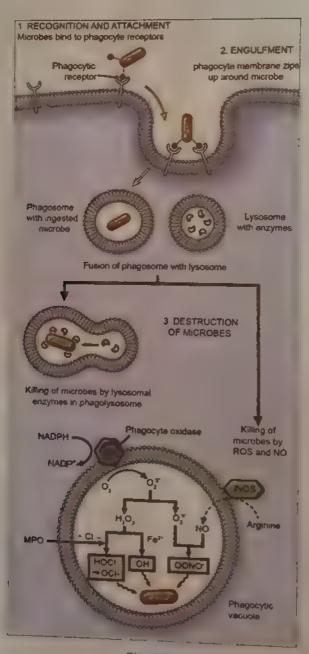


Fig. 3.7.

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Opso bind t i. Fc ii. Cat Plast

Manr Fibrit Fibro

C-Re Neut abse

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Kill

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al cell

icles.

Efficiency of phagocytosis increased by opsonistion.

Opsonins

bind to specific receptors on leukocytes.

i. F<sub>c</sub> fragment of IgG → F<sub>c</sub> gamma R1

ii. C<sub>30</sub> & C<sub>301</sub>→ CR 1, 2,3

plasma proteins:

Mannose binding lectins -> C1q

Fibrinogen

→ Integrins Fibronectin

C-Reactive proteins.

Neutrophils & macrophages: can recognize engulf bacteria & extraneous matter in absence of opsonins (Non- Opsonic phagocytosis).

### Engulfment:

#### Steps:

- Pseudopods of phagocyte flow around the microbe to be engulfed.
- Microbe enclosed in a phagosome.
- Phagosome fuses with lysosome- phagolysosome.
- Degranulation into phagolysosome and bacterial killing.

Biochemical events of engulfment same as chemotaxis.

### Killing / Degradation:

### A. Mainly: O, dependent mechanisms

- Activation of NADPH oxidase (found in neutrophil membrane).
- Requires MPO also.

### HOCI: - Halogenation:

- Perioxidation.
- 1. H<sub>2</sub>O<sub>2</sub>- MPO-halide: most efficient bactericidal system.
- effective against fungi, viruses, protozoa, helminthes.

Dead organisms → lysosomal hydrolases.

- 2. MPO deficient leukocytes: superoxide, hydroxyl singlet oxygen.
- B. O<sub>2</sub> -independent mechanisms: through action of substances in leukocyte granules.
- Bactericidal permeability increasing protein (BPI) phospholipase activation, ↑ permeability of bacterial wall.
- Lysozyme -hydrolyses the glycopeptide coat of bacteria.
- Lactoferrin.
- Major basic protein: Eosinophils.
- Cytotoxic to many parasites.
- Defensins: pH of phagolysosome: 4-5.

### PATHOLOGY

# Release of leukocyte products:

- Lysosomal enzymes: present in granules.
- Oxygen derived active metabolites.
- Products of arachidonic acid metabolism (PGs, LTs).

#### Cause.

- Endotheral injury.
- Tissue damage.
- Regurgitation during feeding: If Phagocytic vacuole remains transiently open to outside.
- Frustrated phagocytosis: on flat surface (e.g. GBM where immune complexes are deposited. The leukocyte is unable to phagocytosis the fixed immune complexes and lysosomal enzyme are released.
- · Surface phagocytosis: Mech. by which phagocytes facilitate ingestion of bacteria and other fore gn material by trapping it against resistant surface.
- Cytotoxic release: After phagocytosis of potentially membranolytic substances (e.g. crystals)

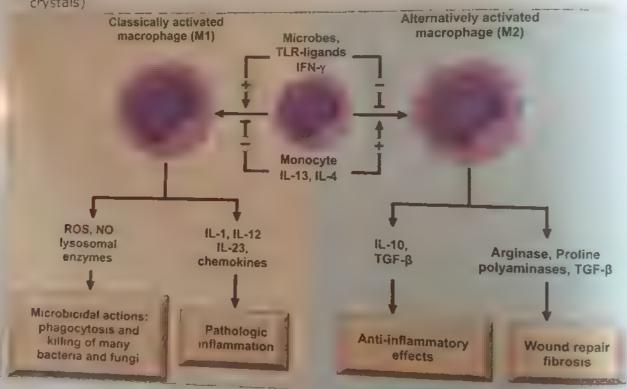


Fig. 3.8:

# Neutrophil Extracellular Traps (Robbins 9th edition- New Topic):

NETs are extracellular fibrillar networks that provide a high concentration of antimicrobial substances at sites of infection and prevent the spread of microbes by trapping them in

They are produced by neutrophils in response to infectious pathogens and inflammatory







Fig. 3.9:

- A. Healthy neutrophils with nuclei stained red and cytoplasm stained green.
- B Release of nuclear material from neutrophils (note that two have lost their nuclei) forming extracellular traps.
- C. An electron micrograph of bacteria (staphylococci) trapped in NETs.

### **Defects in Leukocyte Function**

Defects in leukocyte adhesion:

LAD 1: β chain of CD 11/ CD 18 integrins- repeated bacterial infection/ impaired wound hearing.

\_AD 2: Absent Sialyl Lewis X.

(Milder) (Defective fucosyl transferase).

### Defects in Phagocytosis:

- Chediak Higashi Syndrome.
  - · AR.
- Defective degranulation & delayed microbial killing.
- Neutrophils: Giant granules (in P/S) (aberrant organelle fusion), neutropenia.
- · Disorder in membrane associated protein which is involved in organelle membrane docking & fusion.
- transfer of lysosomal enzymes.
  - 1. To phagocytic vacuoles:
    - 1 infections
  - 2. Melanocytes
- Albinism
- 3. Cells of CNS
- Nerve defects
- 4. Platelets
- Bleeding disorders

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# **Defects of Microbicidal Activity:**

Defects of Microbicidal Activities and the Chronic granulomatous diseases: inherited defect in genes encoding several, component.

Chronic granulomatous diseases: unherited defect in genes encoding several, component. of NADPH oxidase (which generates super oxide).

- X finked: most common.
- · AR

### Others:

- Neutrophil specific granule deficiency.
- Myeloperoxidase deficiency.

Acquired: Thermal injury, malignancy, DM, sepsis, immunodef, etc.

### **Chemical Mediators**

C. H. Danisand		
Cell-Derived Historiane	Mast ceils, basophils. platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasodilation, increased vascular permeability
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fèver
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nunc avide	Endothelium, macrophages	Vascular smooth muscle relaxation, killing of microbes
Cytokines (TNF, IL-1)	Macrophages, endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules), fever/pam anorexia hypotension, decreased vascular resistance (shock)
Mediator	Principal Sources	Actions
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Plasma Protein-Deriv		
Complement products (C5a, C3a, C4a)	Plasma (produced in liver)	
Kinins	Plasma (produced in liver)	Leukocyte chemotaxis and activation,
Proteases activated Juring coagulation	Plasma (produced in liver)	vasodilation (mast cell stimulation)  Increased vascular permeability, smooth muscle contraction, vasodilation, pain
	MAC, membrane attack c	Endothelial activation, leukocyte recruitment

IL-1, interleukin-1; MAC, membrane attack complex; TNF, tumor necrosis factor.

Fig. 3.10: Inflammatory mediators of increased vascular permrability

#### Histamine:

- Performed stores.
- First to be released.
- Widely distributed.
- Richest source: mast cells (present in connective tissue adjacent to BVs).
- · Basophils, Platelets.

#### Release:

- Physical injury (trauma, heat, cold).
- Immune reacts. (Ab. Binding to mast cells).
- C.comp. (C3a & 5a).
- Histamine releasing proteins.
- Neuropetides (substance P).
- Cytokines (IL-1, IL-8).

### Function:

- Dilatation of arterioles (constricts large arteries).
- 1 vascular permeability of venules.
- Immediate phase of ↑ vasc. Perm (via H<sub>1</sub> receptors).

Epi

### Serotonin: (5HT):

Actions similar to histamine.

- present in platelets enterochromaffin cells.
- (Platelet aggregation and Release).

### Plasma Proteases:

Complement System.

20 component proteins.

- Present in greatest concentration plasma.
- Present as inactive forms (C<sub>1</sub> to C<sub>9</sub>).
- Most critical step:

Activation of C, by 3 pathways- classical, lectin and alternate.

- C3 and C5 can also be activated by Plasmin and lysosomal enzymes also.
- C<sub>3a</sub>C<sub>5a</sub> Anaphylotoxins.
- Release histamine form mast cells.
  - C<sub>5a</sub> Chemotactic to Neutrophils, monocytes, eosinophils, basophils.
  - C<sub>3b</sub>, & C<sub>3b</sub> Opsonins.

### **Deficiency of complement:**

- 1. C, deficiency susceptibility to infections which are fatal if not treated.
- 2. C, and C, Deficiency. Association with Autoimmune Diseases e.g. SLE
- MAC Deficiency increase susp. To Neisseria organisms.
  - C system: closely controlled by protein inhibitors.
  - present in host cell membrane
  - Regulation of C, & C, convertase:
  - DAF (Decay accelerating factor).
  - Binding to active C comp. by specific proteins in plasma:
    - C1 INH (absent C1 binding to immune complex and also inhibits serine proteases like kallikrein and Hageman factor).
    - MIRL (Membrane. Inhibitor of reactive lysis) inhibit Membrane attack complex  $(C_c-9)$

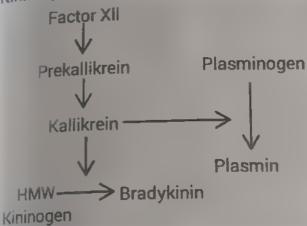
	Distriction ( people and ) is the second
Complement Deficiency	Clinical Association
C3b, iC3b, C5, MBL	Pyogenic bacterial infections
C3, properdin, MAC proteins	Membranoproliferative glomerulonephritis  Neisserial infection
C1 inhibitor	Hereditary angioedema
CD59	Hemolysis, thrombosis
CI q, Cir and Cls, C4, C2	Systemic lupus erythematosus
Factor H and factor I	Hemolytic-uremic syndrome Membranoproliferative glomerulonephritis



PNH: inability to express phosphatidyl-inositol- linked membrane proteins (DAF, MIRL). Hereditary Angioneurotic edema: Deficiency of C1 INH (pptd. by emotional stress / trauma).

Episodic edema-skin, extremities, larynx and intestinal mucosa. Mediator of edema – C2 kinin (proteolytic fragment of  $C_2$  ) and bradykinin.

# Kinin System:



### Bradykinin:

- · Contraction of smooth muscle.
- Dilation of blood vessels (venules).
- · Pain.

#### Kallikrien:

- Activation of F XII → Autocataytic action
- Chemotactic activity.
- Converts C<sub>5</sub> to C<sub>5a</sub>

### **Clotting System:**

Thrombin: Main link between coagulation system and inflammation.

Thrombin binds to PARs - mobilization of P selectin, production of.

Chemokines, expression of endothelial adhesion molecules for integrins, Induction of COX2.

- Fibrinogen Fibrin.
  - vascular permeability.
  - Chemo taxis.

### Hageman factor activates:

- Kinin cascade.
- Coagulation Cascade.
- Fibrinolytic cascade.
- Complement cascade.



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Arachidonic Acid Metabolites:

AA: 20 C polyunsaturated FA (5, 8, 11, 14- eicostatetraenoic acid).

Source



Dietary

Linoleic acid conversion

Found normally esterified in membrane phospholipids.

AA metabolites → Eicosanoids- bind to G-protein coupled receptors on many cells, and mediate inflammation.

- Cyclo- oxygenase  $\rightarrow$  PG $_{\rm s}$  & TX inhibited by NSAID.
- Lipoxygensae → Leukotriene & Lipoxins

Cyclooxygenase pathway: - initiated by 2 enzymes COX 1 & COX 2 produce prostaglandins.

COX1-constitutively expressed in most tissues, also produced in response to inflammator stimuli. In addition to role in inflammation, also has homeostatic function (e.g. Fluid ar electrolyte balance in kidneys, cytoprotection of G1 tract).

COX2 - produced only in response to inflammatory stimuli.

TXA 2: in Platelets (Thromboxane synthase).

- Causes Platelet aggregation and vasoconstriction.
- Unstable, converted to TXB2.

PGI2: in endothelium (Prostacyclin synthetase).

 Vasodilator, inhibits platelet aggregation: 1 vascular permeability chemo tactic effert. PGE2 - hyperalgesic.

Lipoxins: Most recent addition. Involve transcellular biosynthesis (involving 2 to population).

Platelets alone can't form lipoxins (interact with leukocytes).

LXA, & LXB, -> generated by action to platelet 12- Lipoxygenase on neutrophil LTA, LX: Proinflammatory & anti inflammatory actions.

- O inhibit neutrophil chemotaxis & adhesion.
- Stimulate monocyte adhesion.
- Vasodilatation.
- Endogenous negative regulators of leukotriene activity.

Resolvins: New class of AA mediators.

- inhibit leucocytes recruitment and activation by inhibiting cytokine production.
- Aspirin Also acts by stimulating resolvin production.



# Anti-inflammatory therapy:

- Cyclooxygenase inhibitors Aspirin & NSAIDS inhibit COX (not LO) COX2 inhibitorsnewer class of drugs, produce less toxicity than COX1 inhibitors.
- Lipoxygenase inhibitors -newer drugs that inhibit leukotriene production / block leukotriene receptor (Cyst LT1 & cystLT2) used in treatment of asthma.
- Broad spectrum inhibitors Glucocorticoids:

# Down regulate expression of genes for

- COX2.
- Proinflammatory CKs (IL-1 & TNF a)
- Phospholipase A2.
- . INOS.

đ

- Upregulate gene for anti- inflammatory proteins such as lipocortin I (inhibit release of AA from membrane phospholipids).
- . Modify dietary lipids: fish oil.

{(LTs from F.A. in fish oil (Linoleic acid) are less potent than those derived from AA found in most animal/vegetable fats)}

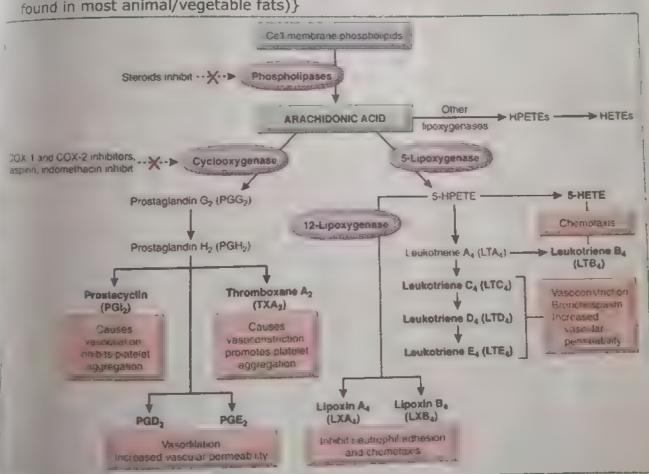


Fig. 3.11:

Fig. 3.12 Cytokines important in inflammation. GM-CSF = granulocyte-macrophage colony-stimulating factor IL= interleukin; NK natural killer; tFN = interferon; TNF = tumor necrosis factor.

Chemokines: - Family of small proteins. Chemo attraction to leucocytes. Four major classes.

**CXC** or  $\alpha$  chemokine- act on neutrophils eg. IL.

 C-C or β chemokines – monocytes chemo attractant protein (MCP -1) macrophage. Inflammatory protein 1 a (MIP-1a) eotaxin, RANTES.

Acts on eosinophils, monocytes, basophils and lymphocytes. Eotaxin selectively recruits eosinophilis.

- C or y chemokines- specific for lymphocyte.
- CX,C
- Fractalkine- both adhesion & chemotactic agent.
- Mediate their activities by binding to G protein linked receptor (CXCR/CCR).
- Serpentine receptors.
- Act as viral Co- receptor for HIV (CXCR<sub>4</sub>, CCR-5).

Nítrous oxide: - 3 different types endothelial, neuronal, cytokine inducible causes. Vasodilator, ↓ platelet adhesion, regulates recruitment of.

Lysosomal constituents: Specific granules & Azurophil granules.



# Specific granules

Lysozyme Lactoferrin A kaline phosphatase Type 4 collagenase Plasminogen activator Phospholipase A2

#### **Azurophil granules**

Lysozyme Defensins Acid hydrolases Neutral proteases Bactericidal factors

- elastase

- non specific collagenase

- cathepsin G

Myeloperoxidase

Phospholipase A2

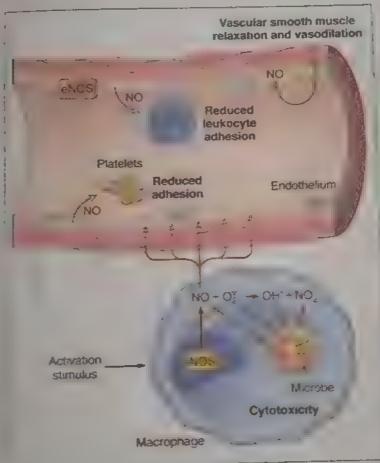


Fig 3.13.

Harmful proteases kept in check by antiproteases-  $\alpha 1$  antitrypsin &  $\alpha$  2 macroglobulin.

### Outcomes of acute inflammation:

- Resolution clearance of injurious stimuli.
  - Clearance of mediators & acute inflammatory cells.
  - Replacement of injured cells.
  - Normal function.

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#### PATHOLOGY 64 1

- Pus formation (Abscess).
- Healing with fibrosis.
- Chronic inflammation.

## Chronic Inflammation:

- Prolonged duration with inflammation, tissue repair and destruction.
- Arise during.
  - Persistent infection by micro organisms.
  - Prolonged exposure to potentially toxic agents.
  - Autoimmunity.

### Histologic features:

- Infiltration by mononuclear cells- macrophage lymphocyte plasma cell.
- Tissue destruction.
- Healing by connective tissue replacement.

Macrophage- Dominant cell of chronic inflammation.

- Part of mononuclear phagocyte system
  - Macrophages in different tissues microglia (CNS), Kupffer cells (Liver), Alveo. macrophages (Lung), osteoclasts (Bone).

Bone marrow stem cell ---

Blood monocyte ---- Tissue macrophage

Mechanism of macrophage accumulation in tissues:

- Recruitment of monocytes from circulation- chemotactic stimuli- chemokines (MCP-1), C5a, PDGF, TGF alpha etc.
- Local proliferation in tissue.
- Immobilization at the site of inflammation.
- After accumulation, macrophages get activated. Activated macrophages release variety of substances, which:
- Kill the injurious agent.
- Cause tissue destruction- hall mark of chronic inflammation.
- Initiate repair.

### Chronic Granulomatous inflammation:

- Distinctive type of chronic inflammation.
- · Granuloma is a microscopic aggregation of macrophages that are transformed into epithelium like cells (Epithelioid cells) surrounded by a collar of mononuclear leucocytes principally lymphocytes. Old granulomas may have an enclosing rim of fibrosis.
- · Granuloma also has giant cells- Langhans type with horse shoe shaped nuclear arrangement or foreign body type with haphazard nuclear arrangement.
- 2 Types of granulomas.

### Foreign body Granuloma:

- Inert foreign bodies sutures, fibers, talc.
- Foreign material in centre of Granuloma.



# immune Granuloma:

- Insoluble microbes that can induce cell mediated immune response.
- INF gamma important in transformation of activated macrophages into epithelioid cell.

# Common Causes:

- . Tuberculosis.
- Leprosy.
- Syphilis.
- . Cat Scratch disease.
- · LGV.
- . Sarcoidosis.
- Some fungal infection.
- · Berylliosis.

# Regeneration And Repair

# Cell Surface Receptors and Associated Signal Transduction Systems:

# Ceel Surface Receptors:

- 1. Receptors with intrinsic tyrosinase enzyme activity.
- 2. Receptors without intrinsic tyrosinase enzyme activity.
- 3. G protein coupled receptors (Seven spanning receptors).

## Signal Transduction Systems:

- 1. MAP Kinase pathway-Ras protein.
- 2. Phosphoinositide 3 Kinase pathway Akt protein.
- 3. Inositol Lipid pathway Phospholipase C.
- cAMP pathway → ↑ Protein kinase A.
- 5. JAK/STAT pathway JAKS (Janus kinases) phosphorylate STAT (signal transducers activators of transcription).

### Transcription Factors:

Signal transduction ⇒ Transfers information to nucleus ⇒ Controlled by transcription factors ⇒ DNA binding domain & Regulatory domain.

Activation domain - e.g. cmyc.

Repression Domain – e.g. p53  $\rightarrow$  ↑ CDKI (p21).

### Cell Cycle Regulators:

### Molecular controls:

Cyclins (proteins) & Cyclin Dependent Kinases (CDKs).

After completion of function: Cyclins→ degraded by ubiquitin – proteasome pathway.

Restriction point: Surveillance mechanism - G1/S.

Cheek points; Sense problem in DNA replication repair, segregation - G1/S and G2/M.

#### Growth Inhibition:

- Contact inhibition.
- Growth suppression.

### E.g. TGF-β↑ CDK.

### Repair By Fibrosis:

- Formation of new blood vessel.
- Migration and proliferation of fibroblasts.
- Deposition of ECM.
- Maturation and organization of fibrous tissue: Remodeling.
- Granulation tissue pink soft granular appearance on surface of wounds fibroblast & vascular endothelial cell proliferation.
- · Wound contraction.

### Angiogenesis:

- Vasculogenesis: Primitive vascular network during embryonic life; dev from angioblasts.
- Angiogenesis / Neovascularization: Pre existing vessels send out capillary buc sprouts to produce new vessels.
  - · Chr. Inflammation.
  - · Tissue repair.
  - Malignancies.

### Steps:

- 1. Proteolytic degradation of BM of vessel.
- 2. Migration of endothelial cells towards angiogenic stimulus.
- 3. Proliferation of endothelial cells behind leading front.
- 4. Maturation of endothelial cells: Capillary tube forming.
- 5. Recruitment of periendothelial cells to support endothelial tubes.

VEGF & Angioproteins (secreted by mesenchymal & stromal cells) – Receptors on endothelial cells.

VEGF + VEGF R2 - new capillary formation (endothelial proliferation).

VEGF + VEGF R1 - Mobilization of endo. Stem cells /? tube formation.

Angiopoietin 1 + tie 2 - recruits periendothelial cells.

Angiopoletin 2 + tie 2 stop signal in absence of VEGF.

PDGF + R - recruitment of smooth muscle cells.

FGF + R - angiogenic factor.

E/c Matrix proteins as regulators of angiogenesis.

- 1. Integrins stabilize.
- matricellular proteins ~ SPARC, tensacin. Thrombospondin → destabilise C M

roblastic

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s on

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3. Proteases.

4 Endostatin → (·) angiogenesis.

1 Emigration and proliferation of fibroblasts at site of injury - TGF, PDGF, EGF, FGF.

2. Deposition of ECM - Affected by collagen deposition / degradation.

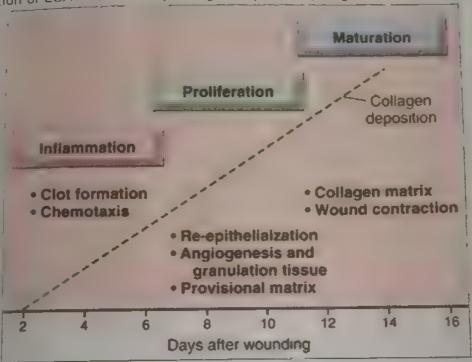


Fig. 3.14:

### Days after wounding:

### 1. Wound healing:

- a. Regeneration and repair of damaged cells tissues starts as soon as the inflammatory process begins.
- b. Wound healing involves two separate processes.
  - i. Regeneration of the damaged tissue by cells of the same type.
  - ii. Tissue repair with replacement by connective tissue.

### 2. Regeneration:

- a. Different tissues have different regenerative capacities.
- b. Labile cells.
- i. Regenerate throughout life.
- ii. Examples: surface epithelial cells (skin and mucosal lining cells), hematopoietic cells, stem cells etc.
- c. Stable cells:
  - i. Replicate at a low level throughout life.

ii.

iii.

iv.

- ii. Have the capacity to divide if stimulated by some initiating event. They are in Go phase and can be stimulated to enter G, phase. iii. Examples: hepatocytes, proximal tubule cells, endothelium etc.
- d. Permanent cells.
  - i. Cannot replicate.
- ii. Example: neurons and cardiac muscle.

### 3. Tissue repair:

- a. Replacement of a damaged area by a connective tissue scar.
- b. Tissue repair is mediated by various growth factors and cytokines.
  - i. Transforming growth factor (TGF-β).
- ii. Platelet derived growth factor (PDGF).
- iii. Fibroblast growth factor (FGF).
- iv. Vascular endothelial growth factor (VEGF).
- v. Epidermal growth factor (EDF).
- vi. Tumor necrosis factor (TNF- $\alpha$ ) and IL-1.

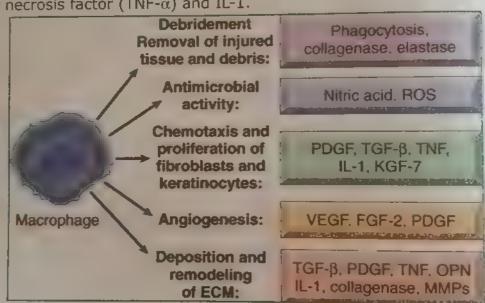


Fig. 3.15:

- c. Granulation tissue.
  - i. Synthetically active fibroblasts.
  - ii. Capillary proliferation.
- d. Wound contraction is mediated by myofibroblasts.
- e. Scar formation.

### Primary union (healing by first intention):

- a. Definition: Occur with clean wounds when there has been little tissue damage and the wound edges are closely approximated.
- b. The classic example is a surgical incision.

### Description of healing wounds:

- A. Healing of a clean, uninfected surgical incision approximated by surgical sutures is k/a.
  - Primary Union- Healing by first intention.





# Involves following changes:

- i. O hours- incision filled with clot (fibrin + blood cells).
- ii. Within 24 hrs-.
  - Neutrophils from margins infiltrate the clot.
  - . Mitosis begins in epithelial basal cells.
- iii. 24 to 48 hrs.
  - Below scale a continuous, but thin epithelial layer is formed.
- iv. Day 3.
  - Neutrophils are replaced by macrophages (MCQ).
  - Granulation tissue begins to appear (MCQ).
  - Epithelial cell proliferation continues.
- v. Day 5.

Incision space is filled with granulation tissue.

- Neovascularisation is maximum (MCQ).
- Collagen fibrils more abundant.
- Epidermis recovers normal thickness with surface keratinization MCQ.

#### vi. WK2.

- Accumulation of collagen and proliferation of fibroblasts.
- (↓ Leukocyte, ↓ edema, regression of vascular channels).

vii. End of 1st month or 2 month-Scar comprises of cellular connective tissue.

#### Tensile Strength:

- 1st wk-Sutures removed 10%. 1s over next 4 wks.
- 3<sup>rd</sup> month Plateau 70-80% of unwounded skin (through life).
- Collagen adult skin type 1; early Granulation tissue type III.

### Healing by Secondary intention:

Occurs when there is more extensive loss of tissue as in infarction, inflammatory, ulceration, abscess and large wounds.

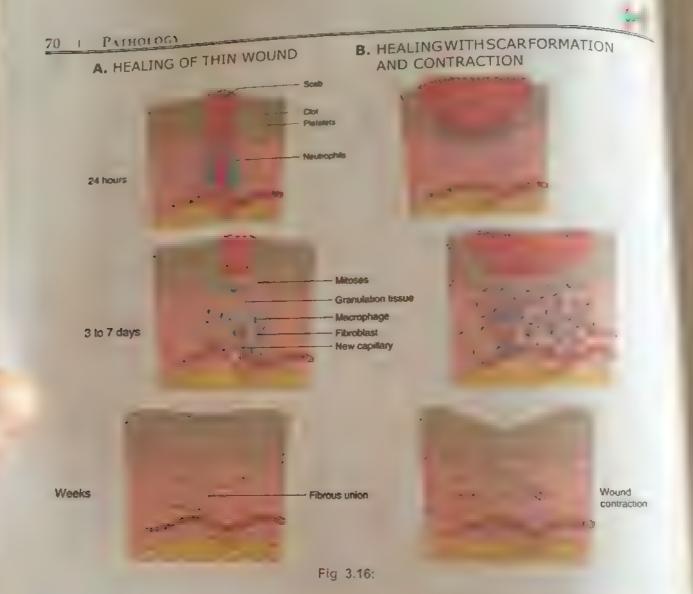
#### Common:

- · Large tissue defect.
- Inflammatory reaction more intense.
- Large amount of granulation tissue formed.
- Large scar.
- Wound contraction Most imp difference b/w 1º and 2º intention.

Remodeling: Balance between collagen deposition and collagenase secretion.

Degradation by Zinc metalloproteinases or collagenase- important for tissue. Remodeling, angiogenesis and cancer metastasis.

- Collagenase produced by fibroblasts, macrophages, neutrophils, synovial cell and some epithelial cells.
- Activated collagenase inhibited by tissue inhibitor of metalloproteinases.



# Pathological Aspects of Repair:

<ul> <li>Fibrin</li> <li>Bleeding disorder</li> <li>Fibronectin</li> <li>↑↑ corticosteroid</li> <li>Dea</li> </ul>	s Delaying Wound
• Estroden	emia ction

ound

Fig. 3.17: The Sequential phases of the heading process

## Aberrations in Wound Healing:

### 1. Delayed wound healing:

a. Wound healing may be prolonged by foreign bodies, infection, ischemia, diabetes, malnutrition, or scurvy.

## 2. Hypertrophic scar:

- a. Results in a prominent scar that is localized to the wound.
- b. Excess production of granulation tissue and collagen.

#### 3. Keloid:

- a. Genetic predisposition.
- b. More common in Africian Americans.
- c. Tends to affect the earlobes, face, neck, sternum, and forearms.

d. May produce large tumor like scars, which often extend beyond the injury site e. Excess production of collagen that is predominantly type III.





Bone

Fig. 3.18:

	Tissue	unta	Matrix Mol	he as tablecadore as
Lissue or Body Fluid	Primary Mesodermal Cell	Prominent Collagen Types	Noncollagenous Matrix Proteins	Glycosaminoglycans Proteoglycans ( PGs)
Plasma			Fibronectm, fibrinogen. vitronectin	Hyaluronan
Dermis Reticular papillary Fpidermal junction	Fibroblast	1, III, V, VI, XII VII, XVII (BP 180). anchoring fibrils, hemidesmosome	Fibronectin, elastin, fibrillin	Hyaluronan, decorin, biglycan, versican
Masele	Muscle cell	1, III, V, VI, VIII, XIII	Fibronectin, elastin, fibrillin	Aggrecan, biglycan, decorin, fibromodulin
Peri , epimysium Aortic med.a adventitia	Fibroblast			
Tendon	Fibroblast	I, III, V, VI, XH	Fibronectin, tenascin (myotendon junction), elastin, fibrillin	Dacorin, biglycan, fibromodulin, lumican, varsıcan
Ligament	Fibroblast	I, III, V, VI	Fibronectin, elastin, fibrillin	Dacorin, biglycan, versican
Cornea	Fibroblast	1, III, V, VI, XII		Lumican, keratocan, mimecan, biglycan, decorin



Cartilage	Chondrocyte hypertrophic cartilage	III, IX, VI, VIII, X, XI	Anchorin Cll.fibronectin, tensein	Hyaluronan, aggrecan, biglycan, decorin, fibromodulin, lu mican, perlecan (minor)
Bone	Osteocyte	I, V	Osteocalcin, ostaoporitin, bone sialoprotain, SPARC {osteonectin}	Decorin, fibromodulin, biglycan
Basement nembrane zones	Epithelial, endothelial adipocytes, Schwann cell, muscle cells (endomysium), pericytes	IV, XV. XVIII	Laminin. nidogen entactin	Heparan sulfate proteoglycans, perlecan  Collagen XVIII (vascular), agrin (neuromuscular junctions)



# CONTRACTO

o Concept 4.1: Neoplasia



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Concept 4.1: Neoplasia

Learning Objectives: Occupational cancers, Oncogenesis, immune response to tumors, Knudson two hit hypothesis, paraneoplastic syndromes, tumor markers

### Time Needed

	1111111		
1× reading		2.5 hours	
1 Icacing		60 - 75 mins	
2 <sup>nd</sup> reading		00 - 75 111113	

In the premolecular era, the eminent British oncologist Willis came closest: "A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change."

# All tumors have two basic components:

- 1. Neoplastic cells that constitute the tumor parenchyma and
- 2. Reactive stoma made up of connective tissue, blood vessels, and variable numbers of cells of the adaptive and innate immune system

Benign Tumors: A tumor is said to be benign when its gross and microscopic appearances are considered relatively innocent, implying that it will remain localized. will not spread to other sites, and is amenable to local surgical removal

Malignant Tumors: Malignant tumors are collectively referred to as cancers, derived from the Latin word for crab, because they tend to adhere to any part that they seize or in an obstinate manner. Malignant tumors can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death

Most important differentiating feature of benign vs. malignant (\*)

Presence of metastasis > invasiveness

Differentiation refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally; lack of differentiation is called anaplasia. Lack of differentiation, or anaplasia, is considered a hallmark of malignancy. The term anaplasia means "to form backward," implying a reversal of differentiation to a more primitive level.

### Lack of differentiation, or anaplasia, is often associated with many other morphologic changes:

- 1, Pleomorphism and tumor giant cells
- 2. Abnormal nuclear morphology: a N:C ratio approaching 1:1 instead of usual 1:4 or 1:6; macro nucleoli and hyper chromatic nuclei
- 3. Mitoses: atypical bizarre mitotic figures
- 4. Loss of polarity: orientation to the basement membrane is disturbed
- 5. Ischemic necrosis, mostly in central areas

The first step toward neoplasia is cellular transformation. The chronic irritation from cigarette smoke has led to an exchanging of one type of epithelium (the normal respiratory epithelium at the right) for another (the more resilient squamous epithelium at the left). Thus, there is metaplasia of normal respiratory laryngeal epithelium to squamous epithelium in response to chronic irritation of smoking.





Fig. 41:



Fig. 4 2:

This is the next step toward neoplasia. Here, there is **normal cervical squamous epithelium** at the left, but **dysplastic squamous epithelium** at the right. The dysplastic epithelial cells are darker, smaller, and more crowded, without an orderly process of maturation. Dysplasia is a disorderly growth of epithelium, but still confined to the epithelium. Dysplasia is still reversible.

Dysplasia: a term that literally means "disordered growth."

It is encountered principally in epithelia and is characterized by a constellation of changes that include loss in the uniformity of the individual cells as well as loss in their architectural orientation.

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Dysplastic cells may exhibit considerable pleomorphism and often contain large hyper chromatic nuclei with a high nuclear-to-cytoplasmic ratio.

The architecture of the tissue may be disorderly.

For example, in dysplastic squamous epithelium the normal progressive maturation of tall cells in the basal layer to flattened squares on the surface may fail in part or entirely, leading to replacement of the epithelium by basal-appearing cells with hyper chromatic nuclei. In addition, mitotic figures are more abundant than in the normal tissue and rather than being confined to the basal layer may instead be seen at all levels, including surface cells.



Fig. 4.3:

At high magnification, the normal cervical squamous epithelium at the left merges into the dysplastic squamous epithelium at the right in which the cells are more disorderly and have darker nuclei with more irregular outlines.

Although dysplasia may be a precursor to malignant transformation, it does not always progress to cancer. With removal of the inciting causes, mild to moderate dysplasia that do not involve the entire thickness of epithelium may be completely reversible.

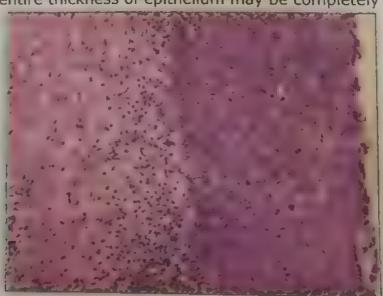


Fig. 4.4:



When an entire portion of epithelium is composed of abnormal cells and no normal when all cells remain, and the process is not potentially reversible, then the process epithelial toward dysplasia and is now neoplasia, which is loss of control of the cellular proliferative process. If the **basement membrane** is still intact, as shown here, then the process is called "carcinoma in situ" because the carcinoma is still confined to the epithelium. A neoplasm arising in epithelium is termed as a carcinoma.

A benign neoplasm looks a lot like the tissue with normal cells from which it originated, and has a slow growth rate. Benign neoplasms do not invade surrounding tissues and they do not metastasize. Thus, characteristics include:

- Slow growth
- Resemblance to tissue of origin (well differentiated)
- Circumscription
- Lack of invasion
- Absence of metastases

A hamartoma is a peculiar benign neoplasm which is a localized but haphazard growth of tissues normally found at a given site (pulmonary hamartoma has jumbled cartilage, bronchial epithelium, and connective tissue)

A choristoma is a benign neoplasm consisting of tissue that is not normal to the site of origin (e.g., salivary gland choristoma of the middle ear).

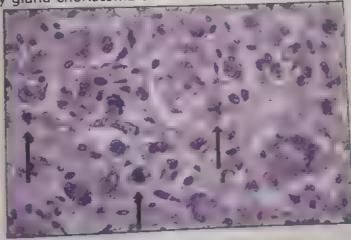


Fig. 4.5:

Here are three abnormal mitoses. Mitoses by themselves are not indicators of malignancy. However, abnormal mitoses are highly indicative of malignancy. The marked pleomorphism and hyperchromatism of surrounding cells also favors malignancy.

Metastasis is defined by the spread of a tumor to sites that are physically discontinuous with the primary tumor, and unequivocally marks a tumor as malignant, as by definition benign neoplasms do not metastasize.

All malignant tumors can metastasize, but some do so very infrequently.

Examples include malignant neoplasms of the glial cells in the central nervous system, called gliomas, and basal cell carcinomas of the skin

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**Pathways of Spread** 

Dissemination of cancers may occur through one of three pathways:

- 1. Direct seeding of body cavities or surfaces,
- 2. Lymphatic spread (most common), and
- 3. Hematogenous spread.

A sentinel lymph node is defined as "the first node in a regional lymphatic basin that receives lymph flow from the primary tumor."

Sentinel node mapping can be done by injection of radiolabeled tracers or colored dyes and examination of frozen sections of the sentinel lymph node performed during surgery can guide the surgeon to the appropriate therapy. Sentinel node examination has also been used for detecting the spread of melanomas, colon cancers, and other tumors.

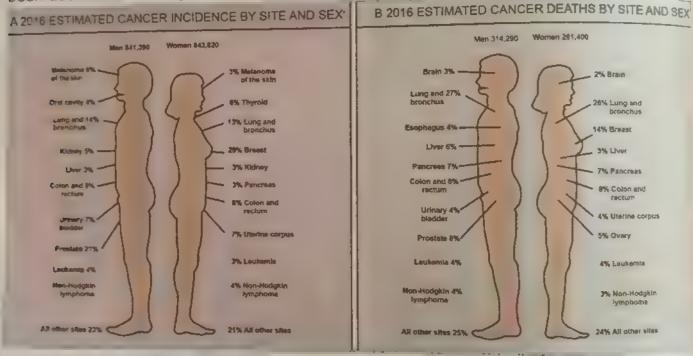


Fig. 4.6:

Arteries, with their thicker walls, are less readily penetrated than are veins.

Understandably the liver and the lungs are most frequently involved in such hematogenous dissemination, because all portal area drainage flows to the liver and all caval blood flows to the lungs. Cancers arising in close proximity to the vertebral column often embolize through the paravertebral plexus, and this pathway is involved in the frequent vertebral metastases of carcinomas of the thyroid and prostate



## ational cancers:

Occupational Carice	Human Cancers for Which Reasonable Evidence is Available	
Arsenic and arsenic compounds	Lung carcinoma skin carcinoma	By-product of metal smelling; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, esophageal, gastric, and colon carcinoma; mesothelioma	Formerly used for many applications because of fire, heal and friction resistance: still found in easting construction as well as fire-resistant testes, friction materials (i.e., brake linings), underlayment and renting papers, and floor uses
Benzene	Acute myeloid leukemia	Principal component of light oil; despite known risk many applications east in printing and lithography, paint rubber, dry clearing, adhesives and coatings, and detergents; formerly widely used as soften) and fumigant
Bervii um and beryllium compounds	Lung carcinoma	Missile fuel and space vehicles. Hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate carcinoma	Uses include yellow pigments and phosphors found in solders; used in batteries and as allowed in metal plating's and coatings
Chromium compounds	Lung carcinoma	Component of metal alloys, paints, pigments and preservatives
Nickel compounds	Lung and oropharyngeal carcinoma	Nickel plating: component of ferrous alloys ceramics, and batteries; by-product of stainless-steel and welding
Radon and its decay products	Lung carcinoma	From decay of minerals containing uranium potentially serious hazard in quarries and underground mines
Vinyl chloride	Hepatic angiosarcoma	Refrigerant; monomer for vinyl polymers: adhesive for pasties; formerly inert aerosol propellant in pressurized containers

Modified from Stellman JM, Stelman SD: Cancer and workplace

# Sing?

Chronic	inflammatory	states an	d cancer:
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Chronic innaminatory		L'iologie Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic careinoma	Alcoholism, germ line mutation, {e.g., in (ho trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder atones
Reflax esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opistorenis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes (Opisthore) viverrim)
Gastritis, ulcers	Gastric adenocarcinoma, MALT lymphoma	Helicobacter pylori
Hepatitis Hepatocellular carcinoma Hepatitis B and or C virus		
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chrome cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis
Adapted from Tlsty 1D, Coussens Pathol Mech Dis 2006, 1.119	LM: Timor stroma and regulation	of cancer development. Ann Ro

## Molecular Basis of Cancer

Certain "genomic themes" haveemerged that are likely relevant to every cancer

- 1. Nonlethal genetic damage lies at the heart of carcinogenesis.
- 2. Tumor is formed by the clonal expansion of a single precursor cell that has incurred genetic damage (i.e., tumors are clonal).



3 Four classes of normal regulatory genes-the growth promoting proto-oncogenes, the growth-inhibiting tumor suppressor genes, genes that regulate programmed the growth analysis), and genes involved in DNA repair-are the principal targets of cell death (apoptosis).

4. Carcinogenesis results from the accumulation of complementary mutations in a

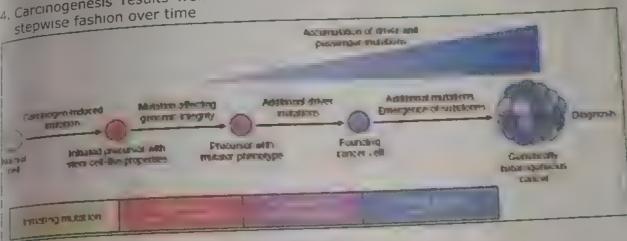


Fig. 4.7:

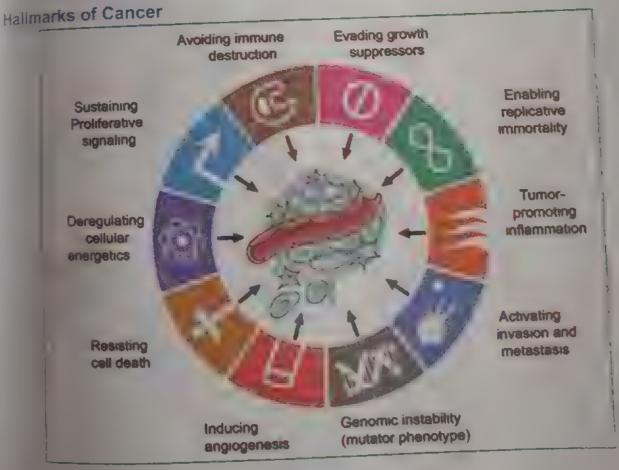
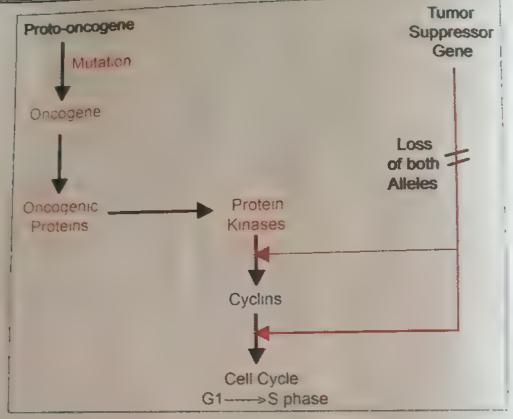


Fig 4.8:



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Fig. 4.9:

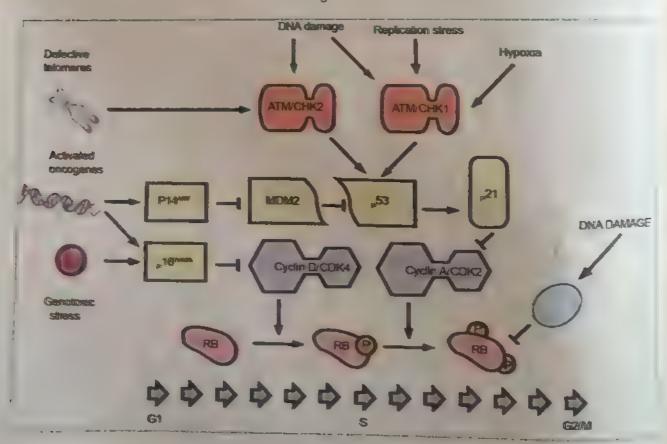


Fig. 4.10:

Suit.

GI pathways that can trigger cell cycle arrest, senescence, or apoptosis. A variety of threats to genomic integrity lead to activation of pathways that result in cell cycle arrest. Signalling via ATM/CHK2 and ATR/CHK1 leads to p53 activation, among other effects. One of the principle downstream effects of p53 is activation of p2 1 expression, with resultant cyclin E (A)/CDK2 inhibition and cell cycle arrest. Senescence, which results in a more sustained cell cycle exit, also involves the up-regulation of p1 4ARF and p1 in a more sustained cell cycle exit, also involves the up-regulation of p1 4ARF and p1 in a more sustained cell cycle exit, also involves the up-regulation of p1 4ARF and p1 arrest via cyclin/CDK inhibition. In response to DNA damage during S phase, activation of p2A can lead to dephosphorylation of RB and inhibition of DNA synthesis.

Laborited Genome Maintenance Defects with Cancer Predisposition

	terrance Derects with Outroof	
heckpoint response	Li Fraument Familial breast cancer	p53. CHK2
peckbeum rech	Retinoblastoma	BRCA1, CHK2
	Familial melanoma	RB
		pl6'NK4A
h rangif	HNPCC/Lynch syndrome	MLH1, MSH2,
Asmatch repair		PMS2, MSH6
- I - WARRION TRIPAIT	Xeroderma pigmentosa	XP genes
Nucleotide excision repair	Ataxia telangiectasia	ATM
OSB response repair	AT-like disorder	MR Ell
	Nijmegen breakage	NBS1
	Fanconi anemia	Pane genes
	Familial breast cancer	BRCA1, BRCA2
	Palmiras Orvania	CHK2, PALB2
CID, rare lymphoma		
Artemis	SCID, rare leukemia	LigaselV
		BLM
lel.case activity	Bloom	WRN
	Werner	RECQ4
	Rothmund Thomson	BUBIB
Mitotic checkpoint	Mosaic variegated aneuploidy	BOBIB

HNPCC, hereditary nonpolyposis colorectal cancer; DSB, double-strand break; AT, ataxia telangiectasia; SCID, severe combined immunodeficiency.

-		All Salambian and the Control of the
	Action	Example
Mechanism  Growth Promotion	Overexpression of growth factor receptors (such as epidermal growth factor, or EGF) making cells more sensitive to growth	HER2 (c-erb B2)
	Increased growth factor signal transduction by an oncogene that lacks the GTPase activity that limits GTP induction of cytoplasmic kinases that drive cell growth	RAS
	Overexpression of a gene product by stimulation from an oncogene (such as RAS)	C-SIS
	Lack of normal gene regulation through translocation of a gene where it is controlled by surrounding genes to a place where it is no longer inhibited	BCR-ABL
	Binding of oncogene product to the nucleus with DNA transcriptional activation to promote entry into the cell cycle	C-MYC
Loss of Tumor	Loss of normal growth inhibition	BRCA-1
Suppressor Gene Function	Lack of regulation of cell adhesion with loss of growth control through cell interaction	APC
	Loss of down-regulation of growth promoting signal transduction	NF-1
	Loss of regulation of cell cycle activation through sequestration of transcriptional factors	RB
	Loss of regulation of cell cycle activation through lack of inhibition of cell proliferation that allows DNA repair	p53
Limitation of Apoptosis	Overexpression of gene, activated by translocation, prevents apoptosis	BCL-2

# Oncogenes

Genes that promote autonomous cell growth in cancer cells are called oncogenes, and their unmutated cellular counter parts are called proto-oncogenes. Oncogenes are created by mutations in proto-oncogenes and encode proteins called oncoproteins that have the ability to promote cell growth in the absence of normal growth-promoting signals.

Oncogenes most commonly and importantly implicated (very important table for exams)

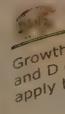
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2		Georgia Kaciars	
DGF-βchain	PDGFB	Overexpression	Astrocytoma
	wth HST1	Overexpression	Osteosarcoma
J. H.	FGF3	Amplification	Stomach cancer
			Bladder cancer
			Breast cancer
			Melanoma
·GF-a	TGFA	Overexpression	Astrocytomas

# HGF Overexpression Hepatocellular carcinomas Thyroid cancer

		Growth Factor Receptors	
EGF-receptor tami.y	ERBB1 (EGFR) ERBB2 (HER)	Mutation Amplification	Adenocarcinoma of lung Breast carcinoma
FMN-Like prosine kinase	FLT3	Point mutation	L eukemia
Receptor tor neurotrophic factors	RET	Point mutation	Multiple endocrine neoplasia 2A and B familial medullary thyroid carcinomas
PDCA receptor	PDGFRB	Overexpression. translocation	Gliomas, leukemias
Receptor for KJT ligand	KIT	Point mutation	Gastrointestinal stromal tumors, seminomas, leukemias
ALK receptor	ALK	Translocation, fusion gene formation Point mutation	Adenocarcinoma of lung, certain lymphomas Neuroblastoma

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GTP-binding	KRAS	Point mutation	Colon, lung, and pancreatic tum and
(G proteins	HRAS	Point mutation	Bladder and kidney tumors
	WHS	Point mutation	Melanomas, hematologic malignancies
	GNAO	Point mutation	Uveal melanoma
	GNAS	Point mutation	Pituitary adenoma, other endoct tumors
Nonreceptor tyrosine	ABL	Translocation	Chronic myelogenous leukemia
kınase		Point mutation	Acute lymphoblastic leukemia
RAN signal transduction	BRAF	Point mutation. Translocation	Melanomas, leukemias, colon carcinoma, others
Notch signal transduction	N0TCH1	Point mutation, Translocation	Leukemias, lymphomas* breast carcinoma
		Gene rearrangement	
JAK STAT signal	JAK2	Translocation	Myeloproliferative disorders
transduction			Acute lymphoblastic leukemia
Nuclear Regulato	ry Proteins		
Transcriptional activators	MYC	Translocation	Burkitt lymphoma
	NMYG	Amplification	Neuroblastoma
Cell Cycle Regu.;	Blors		
Cyclins	CCND1 (Cyclin Dl)	Franslocation	Mantle cell lymphoma, muluple myeloma
		Amplification	Breast and esophageal cancers
Cyclin- dependent kinase	CDK4	Amplification or point mutation	Glioblastoma, melanoma, sarcon



Growth factor signaling pathways in cancer. Growth factor receptors, RAS, PI3K, MYC, Growth factor receptors, RAS, PI3K, MYC, and D cyclins are oncoproteins that are activated by mutations in various cancers. GAPs and D cyclins in various can apply brakes to RAS activation, and PTEN serves the same function for PI3K

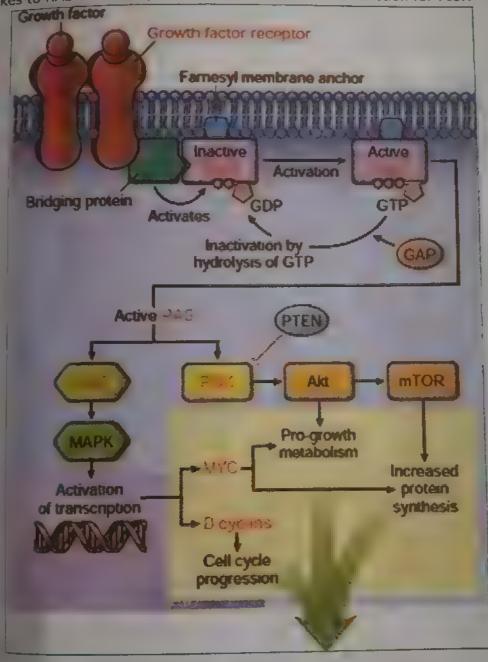


Fig. 4.11:

Growth factor signaling pathways in cancer. Growth factor receptors, RAS, PI3K, MYC, and D cyclins are oncoproteins that are activated by mutations in various cancers. GAPs apply brakes to RAS activation, and PTEN serves the same function for PI3K

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- Point mutations of RAS family genes constitute the most common type of abnormality involving proto-oncogenes in human tumors Approximately 15% to 20% of all human tumors express mutated RAS proteins
- Approximately 15% to 25%.
   RAS proteins are members of a family of membrane-associated small G proteins.
   RAS proteins are members of a family of membrane-associated small G proteins. RAS proteins are members of a total guanosine triphosphate [GTP] and guanosine that bind guanosine nucleotides (guanosine triphosphate [GTP] and guanosine triphospha that bind guanosine indirectors (grant trimolecular proteins. They normally floring state in which thou is a state in the state back and forth between an excited signal-transmitting state in which they are bound to GTP and a quiescent state in which they are bound to GDP
- Stimulation of receptor tyrosine kinases by growth factors leads to exchange of GCP for GTP and subsequent conformational changes that generate active RAS, which in turn stimulates both the MAPK and PI3K/AKT arms of the receptor tyrosine kinase signaling pathway.
- Activation of RAS is transient because RAS has an intrinsic GTPase activity that s accelerated by GTPase-activating proteins (GAPs), which bind to the active RAS and augment its GTPase activity by more than 1000-fold, thereby terminating signal transduction. Thus, GAPs prevent uncontrolled RAS activity
- The consequences of gain-of-function mutations in RAS proteins should be mimicked by loss-of-function mutations in GAPs that normally restrain RAS activity.
- Indeed, disabling mutations of neurofibromin 1, a GAP encoded by the NF1 gene, are associated with the inherited cancer syndrome familial neurofibromatosis type 1

## Oncogenic BRAF and PI3K Mutations

- . Mutations in BRAF, a member of the RAF family, have been detected in close to 100% of hairy cell leukemias, more than 60% of melanomas, 80% of benian nevi, and a smaller percentage of a wide variety of other neoplasms, including co carcinomas and dendritic cell tumors.
- BRAF is a serine/threonine protein kinase that sits at the top of a cascade of other serine/threonine kinases of the MAPK family.
- Like activating RAS mutations, activating mutations in BRAF stimulate each of these downstream kinases and ultimately activate transcription factors. Mutations in other MAPK family members downstream of BRAF are uncommon in cancer, suggesting on y mutations affecting factors near the top of the RAS/MAPK cascade produce significant pro-growth signals in most cell types.
- PI3K is heterodimer comprised of a regulatory subunit and a catalytic subunit, of which several tissue-specific isoforms exist. Under normal circumstances, PI3K is recruited by receptor tyrosine kinase activation to plasma membrane associated signaling protein complexes

# **Alterations in Nonreceptor Tyrosine Kinases**

Mutations that confer oncogenic activity occur in several non receptor tyrosine kinases that normally localize to the cytoplasm or the nucleus.

In many instances the mutations take the form of chromosomal translocations of rearrangements that create fusion genes encoding constitutively active tyrosine kinases. Fran Tran REL Of t

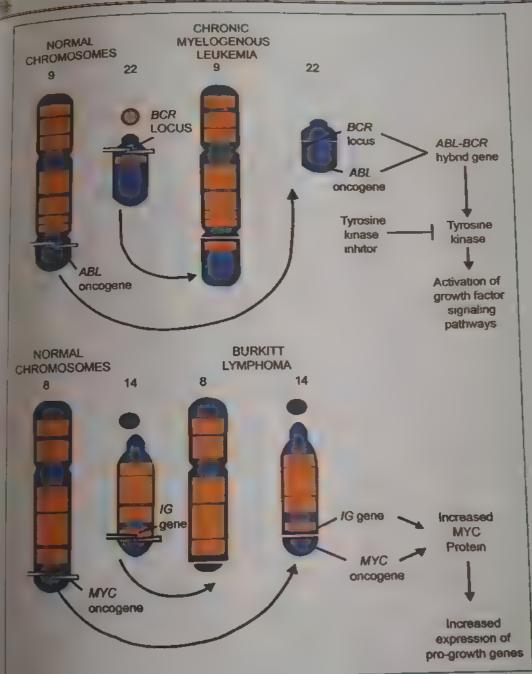


Fig. 4.12:

Transcription Factors

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Transcription factors of this class include the products of the MYC, MYB, JUN, FOS, and REL proto-oncogenes.

Of these, MYC is most commonly involved in human tumors

MYC activates the expression of many genes that are involved in cell growth

- In some contexts, MYC up regulates expression of telomerase In some contexts, Mrc up regulated for the some contexts, Mrc up regulated for factors that can act together to reprogram
   MYC is one of a handful of transcription factors that can act together to reprogram

somatic cells into pluripotent stem cells

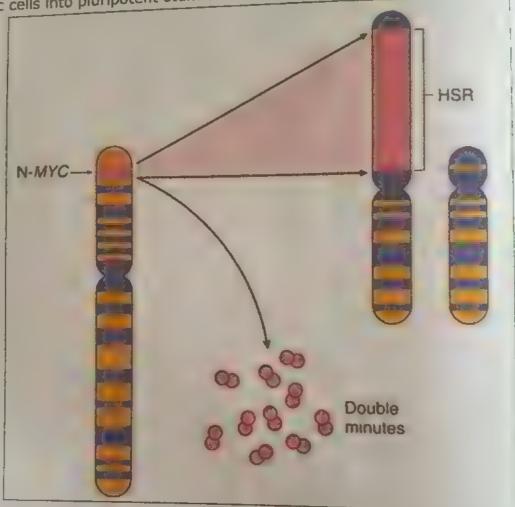


Fig. 4.13:

Amplification of the NMYC gene in human neuroblastomas.

The NMYC gene, normally present on chromosome 2p, becomes amplified and is seen either as extra chromosomal double minutes or as a chromosomally integrated, homogeneous staining region (HSR). The integration involves other autosomes, such as Su

reprogré.

Cyclins and Cyclin-De	Mailur Russetten III
Cyclins and Cyclin-Depende	nt Kınases
CDK4, D cyclins	Form a complex that phosphorylates RB, allowing the cell to progress through the G1 restriction point
Cell Cycle Inhibitors	
CIP/KIP family: p21, p27 CDKNIA-D)	Block the cell cycle by binding to cyclln-CDK complexes p21 Is Induced by the tumor suppressor p53 p27 responds to growth suppressors such as TGF-IJ
NK4/ARF family CDKN2A-C}	p16/INK4a binds to cyclin D-CDK4 and promotes the inhibitory effects of RB p14 ARF increases p53 levels by Inhibiting MDM2 activity
Cell Cycle Checkpoint Comp	oonenis
IB	Tumor suppressive "pocket" protein that binds E2F transcription factors in Its hypophosphorylated state, preventing G./S transition; also Interacts with several transcription factors that regulate differentiation
	Tumor suppressor altered in the majority of cancers; causes cell cycle arrest and apoptosis. Acts mainly through p21 to cause cell cycle arrest. Causes apoptosis by inducing the transcription of pro-apoptotic genes such as BAX. Levels of p53 are negatively regulated by MDM2 through a feedback loop. p53 is required tor the G1/S checkpoint and is a main component of the G2/M checkpoint.

# Tumor suppressor genes

Whereas oncogenes drive the proliferation of cells, the products of most tumor suppressor genes apply brakes to cell proliferation, and abnormalities in these genes lead to failure of growth inhibition, another fundamental hallmark of carcinogenesis

Approximately 40% of retinoblastomas are familial, with the predisposition to develop the tumor being transmitted as an autosomal dominant trait. Carriers of the retinoblastoma trait have a10,000-fold increased risk of developing retinoblastoma (often in both eyes) as compared to the general population, and are also at greatly increased risk of developing osteosarcoma (\*) and other soft-tissue sarcomas. About 60% of retinoblastomas occur sporadically (virtually always in only one eye), and such patients are not at increased risk for other forms of cancer. To explain these two patterns of occurrence of retinoblastoma, Knudson proposed his now canonic "two-hit" hypothesis of oncogenesis. In molecular terms, Knudson's hypothesis can be stated

- 1. Two mutations (hits), involving both alleles of RB at chromosome locus 13q14, are
- 2. In familial cases, children inherit one defective copy of the RB gene in the germ line (the first hit), and the other copy is normal

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- 3. Retinoblastoma develops when the normal RB allele is mutated in retinoblasts as a result of a spontaneous somatic mutation (the second hit)
- 4. In sporadic cases both normal RB alleles must undergo somatic mutation in the same retinoblast (two hits). The probability of this event is low (explaining why retinoblastoma is an uncommon tumor in the general population), but the end result is the same: a retinal cell that has completely lost RB function and becomes cancerous.

Note that a child carrying an inherited mutant RB allele in all somatic cells is perfectly normal (except for the increased risk of developing cancer); it follows that one defective RB gene does not affect cell behavior. Thus, while the genetic trait (increased cancer risk) associated with germ line mutations in RB is inherited in an autosomal dominant fashion, at the level of the individual cell, loss of function mutations in the RB gene behave in a recessive fashion

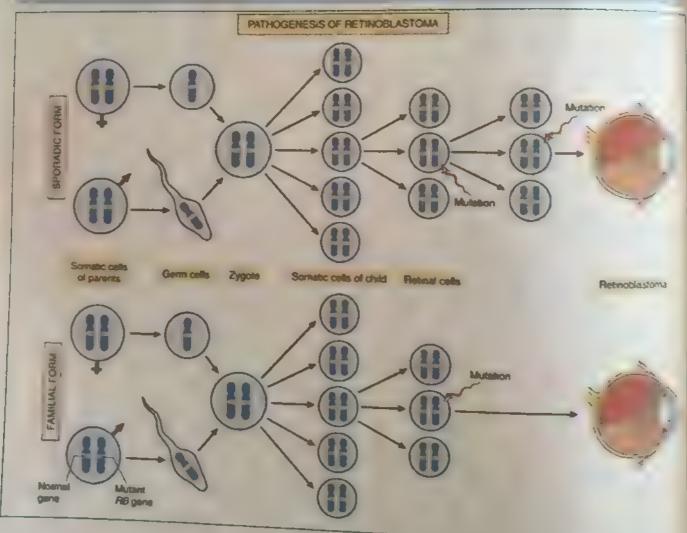


Fig. 4.14:

Jan -				NEOPLASIA 1 22
		Mahikitari Militager	ite signaling pathways	
APC	Adenomatous polyposis coli protein	Inhibitor of WNT signaling	Familial colonic polyps and carcinomas	Carcinomas of stomach, pancreas, melanoma
XI 1	Neuro- fibromin-1	Inhibitor of RAS MAPK Signaling	Neurofibromatosis type 1 (neurofibromas and Malignant peripheral Nerve sheath tumors)	Neuroblastoma, juvenile myeloid leukemia
NF2	Merlm	Cytoskeletal stability, Hippo Pathway signaling	Neurofibromatosis type 2 (acoustic schwannoma and meningioma)	Schwannoma, meningioma
PICH	Patched	Inhibitor of Hedgehog signaling	Gorlin syndrome (basal cell carcinoma, medulloblastoma, several benign tumors)	Basal cell carcinoma, medulloblastoma
PIEN	Phosphatase and tensin homologue	Inhibitor of PI3K/ AKT signaling	Cowden syndrome (variety of being skin, GI, and CNS growths, breast, endometrial, and thyroid carcinoma)	Diverse cancers, particularly carcinomas and lymphoid tumors
ATAD2. ATAD4	SMAD2, SMAD4	Component of the TGF\$\beta\$ signaling pathway, repressors of MYC and CDK4 expression, inducers of CDK inhibitor expression	Juvenile polyposis	Frequently mutated (along with other components of the TGFβ signaling pathway) in colonic ar pancreatic carcinoma

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RB	Retinoblastoma (RBI protein	Inhibitor of G,/S transition during cell cycle progression	Familial retinoblastoma syndrome (retinoblastoma, osteosarcoma, other sarcomas)	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung
CDKN2A	p16/INK4a and p14/ARF	p16: Negative regulator of cyclln-dependent kinases; p14, Indirect activator of p53	Familial melanoma	Pancreatic, breast, and esophageal carcinoma, melanoma, certain leukemia

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98 [	PATHOLOGY	crowth There are	Metabolism and Angiogene	Name .
VHL	Von Hippel Lindau (VHL) protein	Inhibitor of hypoxia- Induced transcription factors (e.g., HF1a	Von Hippel Lindau syndrome (cerebellar hemangloblastoma, retinal angioma, renal cell carcinoma)	Renal cell carcinoma
STKII	Liver kinase B1 (LKB1) or SFK11	Activator of AMPK family of kinases; suppresses cell growth when eel nutrient and energy levels are low	Peutz-Jeghers syndrome (Gl polyps, Gl cancers, pancreatic carcinoma and other carcinomas)	Diverse carcinomas (5%-20% of cases, depending on type)
SDHB. SDHD	Succinate dehydrogenase complex submits B and D	TCA cycle, oxidative phosphorylation	Familial paraganglioma, familial pheochromocytoma	Paragan glioma
	and a second second			

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CDH1	E-cadherin	Cell adhesion, inhibition	Familial	gastric	Gastric	carcinoma,	lobu.ar
,	1	of cell motility	cancer		breast ca	arcinoma	

4		LHADICIS OF GERMINIC			
TP53	p53 protein	Cell cycle arrest and apoptosis in response to DNA damage	21 -	syndrome	human

		1000 004		the control of the co
BRCA1, BRCA2	Breast cancer-1 and breast cancer-2 (BRCA1 and BRCA2)	Repair of double- stranded breaks in DNA	Familial breast and ovarian carcinoma; carcinomas of male breast; chronic lymphocytic leukemia (BRCA2)	Rare
MSH2, MLH1, MSH6	MSH1, MLH1, MSH6	DNA mismatch repair	Hereditary nonpolyposis colon carcinoma	Colonic and endometrial carcinoma

			Juknown Mechanisms	
WT1	Wilms tumor-1 (WT1)	Transcription factor	Familial Wilms tumor	Wilms tumor, certain leukemias
MENI	Menin	Transcription factor	Multiple endocrine neoplasia-1 (MEN1: pituitary, parathyroid, and pancreatic endocrine tumors)	Pituitary, parathyroid, and pancreatic endocrine tumors

# **RB:** Governor of Proliferation

RB, a key negative regulator of the G1 /S cell cycle transition, is directly or indirectly inactivated in most human cancers

RB function may be compromised in two different ways:

- Loss-of-function mutations involving both RB alleles
- A shift from the active hypophosphorylated state to the inactive hyper phosphorylated state by gain-of-function mutations that up regulate CDK/cyclin D activity or by loss-of-function mutations that abrogate the activity of CDK inhibitors

cycli

Fig. 4.15:

E2F S phase

genes

Transcriptional

activation

site

# The Role of RB in Regulating the G1-S Checkpoint of the Cell Cycle.

S phase

**Transcriptional** 

block

E2F

Hypophosphorylated RB in complex with the E2F transcription factors binds to DNA, recruits chromatin-remodeling factors (histone deacetylases and histone methyltransferases), and inhibits transcription of genes whose products are required for the S phase of the cell cycle. When RB is phosphorylated by the cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 complexes, it releases E2F. The latter then activates transcription of S-phase genes. The phosphorylation of RB is inhibited by cyclin-dependent kinase inhibitors, because they inactivate cyclin-CDK complexes. Virtually all cancer cells show

disregulation of the G1-S checkpoint as a result of mutation in one of four genes that disregulation of the phosphorylation of RB; these genes are RB, CDK4, the genes encoding ovon D proteins, and CDKN2A

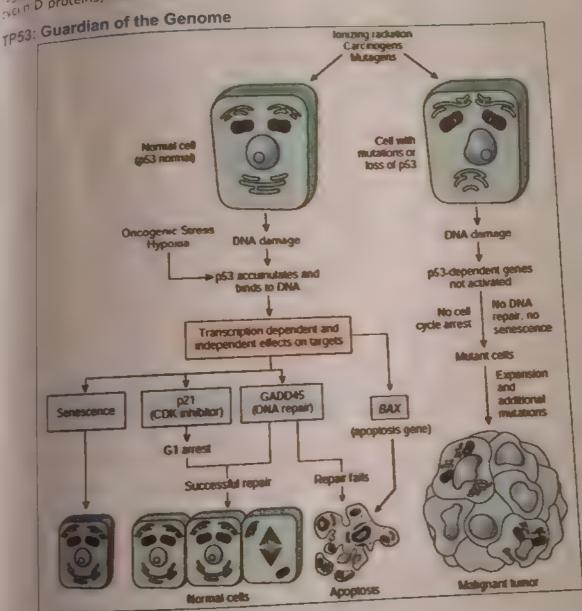


Fig. 4.16:

TP53, a tumor suppressor gene that regulates cell cycle progression, DNA repair, cellular senescence, and apoptosis, is the most frequently mutated gene in human cancers Loss-of-function mutations in TP53, located on chromosome 17p13.1, are found in

Inheritance of a mutated copy of TP53 predisposes individuals to malignant tumors because only one additional "hit" in the lone normal allele is needed to abrogate TP53 function. Such individuals, said to have the Li-Fraumeni syndrome, have a 25-fold greater chance of developing a malignant tumor by age 50 than the general population.



# APC: Gatekeeper of Colonic Neoplasia

Germ line loss-of-function mutations involving the APC (5q21) locus are associated with Germ line loss-of-function motations at the loss of adenomatous polyposis, an autosomal dominant disorder in which individuals familial adenomatous polypusis, an action and adenomatous polyps in the colon born with one mutant allele develop thousands of adenomatous polyps in the colon

APC is a component of the WNT signaling pathway, which has a major role in control no

cell fate, adhesion, and cell polarity during embryonic development WNT signals through a family of cell surface receptors called frizzled (FRZ), and

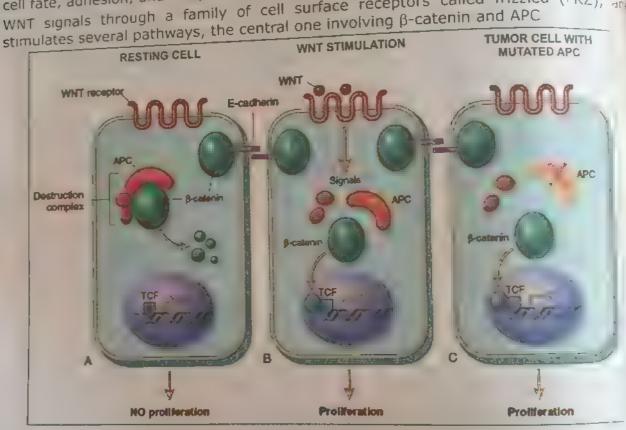


Fig. 4.17:

The role of APC in regulating the stability and function of β-catenin. APC and β-catenin are components of the WNT signaling pathway.

A, in resting colonic epithelial cells (not exposed to WNT), β-catenin forms a macromolecular complex containing the APC protein. This complex leads to the destruction of  $\beta$ -catenin, and intracellular levels of  $\beta$ -catenin are low.

B, when normal colonic epithelial cells are stimulated by WNT molecules, the destruction complex is deactivated, β-catenin degradation does not occur, and cytoplasmic levels increase. β-catenin translocates to the nucleus, where it binds to TCF, a transcription factor that activates genes involved in cell cycle progression.

C, When APC is mutated or absent, as frequently occurs in colonic polyps and cancers, the destruction of  $\beta$ -catenin cannot occur.  $\beta$ -catenin translocates to the nucleus and coactivates genes that promote entry into the cell cycle, and cells behave as if they are under constant stimulation by the WNT pathway.

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β-catenin binds to the cytoplasmic tail of E-cadherin, a cell surface protein that maintains inter cellular adhesiveness.

Loss of cell-cell contact, such as in awound or injury to the epithelium, disrupts the Interaction between E-cadherin and  $\beta$ -catenin, and also promotes increased translocation of  $\beta$ -catenin to the nucleus, where it stimulates genes that promote proliferation; this is an appropriate response to injury that can help repair the wound.

Loss-of contact inhibition, by mutation of the E-cadherin/β-catenin axis, or by other changes, is a key characteristic of carcinomas

Germ line loss of-function mutations of the E-cadherin gene, known as CDH1, cause familial gastric carcinoma, and a variable proportion of sporadic gastric carcinomas are also associated with loss of E-cadherin expression

### CDKN2A

The CDKN2A gene locus encodes two protein products:

- 1 p16/INK4a cyclin-dependent kinase inhibitor, which blocks CDK4/cyclin D-mediated phosphorylation of RB, thereby reinforcing the RB checkpoint; and
- 2 p14/ARF, which activates the p53 pathway by inhibiting MDM2and preventing destruction of p53

Thus, mutation or silencing of CDKN2A impacts both the RB and p53 tumor suppressor pathways

### TGF-β Pathway

In most normal epithelial, endothelial, and hematopoietic cells, TGF-β is a potent inhibitor of proliferation.

It regulates cellular processes by binding to TGF-β receptors I and II.

Dimerization of the receptor upon ligand binding initiates intracellular signals that involve proteins of the SMAD family

Under normal circumstances, these signals turn on antiproliferative genes (e.g., genes for cyclin-dependent kinase inhibitors) and turn off genes that drive cell growth

Mutations affecting the type IITGF-β receptor are common in cancers of the colon, stomach, and endometrium, while mutational inactivation of SMAD4 is common in pancreatic cancers

#### FIER

PTEN (phosphatase and tensin homologue) is a membrane-associated phosphatase encoded by a gene on chromosome 10q23 that is mutated in Cowden syndrome, an autosomal dominant disorder marked by frequent benign growths

PTEN acts as a tumor suppressor by serving as a brake on the PI3K/AKT arm of the receptor tyrosine kinase pathway

#### NF1

Individuals who inherit one mutant allele of the NF1gene develop numerous benign neurofibromas and optic nerve gliomas as a result of inactivation of the second copy of the gene. This condition is called neurofibromatosis type 1

#### NEZ

Germ line mutations in the NF2 gene predispose to the development of neurofibromatosis type 2

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The product of the NF2 gene, called neurofibromin2 or merlin, is structurally similar to the red cell membrane cytoskeletal protein 4.1

#### WT1

Loss-of-function mutations in the **WT1** gene, located on chromosome 11p13, is associated with the development of Wilms tumor

The WT1 protein is a transcriptional activator of genes involved in renal and gonada differentiation. It regulates the mesenchymal-to-epithelial transition that occurs in kidney development

Interestingly, although WT1 is a tumor suppressor in Wilms' tumor, a variety of adult cancers, including leukemias and breast carcinomas, overexpress WT1

### PATCHED (PTCH)

PTCH1 is a tumor suppressor gene that encodes a cell membrane protein called PATCHED1.

PATCHED proteins are negative regulators of the Hedgehog signaling pathway

Germ line loss-of-function mutations in **PTCH1** cause Gorlin syndrome, an inherited condition also known as nevoid basal cell carcinoma syndrome

#### VHL

Encodes a component of a ubiquitin ligase that is responsible for degradation of hypoxia-induced factors (HIFs), transcription factors that alter gene expression in response to hypoxia

- Germ line loss-of-function mutations cause von Hippel-Lindau syndrome, autosomal dominant disorder associated with a high risk of renal cell carcinoma and pheochromocytoma
- Acquired biallelic loss-of mutations are common in sporadic renal cell carcinoma

# The Warberg Effect

Even in the presence of ample oxygen, cancer cells demonstrate distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactose (fermentation) via the glycolytic pathway.

This phenomenon, called the **Warburg effect** and also known as **aerobic glycolysis**, has been recognized for many years (Otto Warburg received the Nobel Prize in 1931 for discovery of the effect that bears his name).

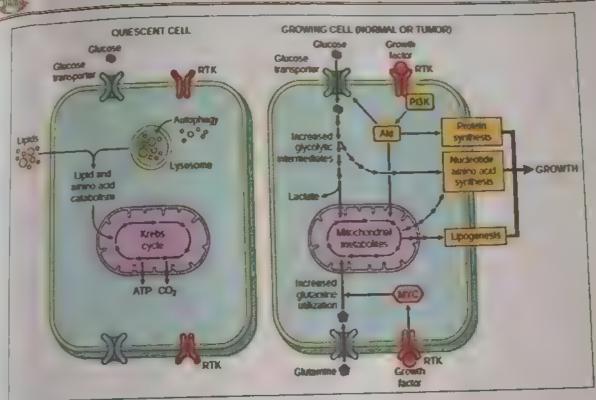


Fig. 4.18:

Quescent cells rely mainly on the Krebs cycle for ATP production; if starved, autophagy (se f-eating) is induced to provide a source of fuel. When stimulated by growth factors, normal cells markedly up regulate glucose and glutamine uptake, which provide carbon sources for synthesis of nucleotides, proteins, and lipids. In cancers, oncogenic mutations involving growth factor signaling pathways and other key factors such as MYC deregulate these metabolic pathways, an alteration known as the Warburg effect.

### **Evasion of Apoptosis**

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- Apoptosis can be initiated through intrinsic or extrinsic pathways, both of which result in the activation of a proteolytic cascade of caspases that destroys the cell.
- Abnormalities of both pathways are found in cancer cells, but lesions that incapacitate the intrinsic (mitochondrial) pathway appear to be most common.
- in greater than 85% of follicular B-cell lymphomas, the anti-apoptotic gene BCL2 is overexpressed due to a (14; 18) translocation.
- Overexpression of other BCL2 family members such asMCL-1 is also linked to cancer cell survival and drug resistance.

Fig. 4.19;

Escape of cells from senescence and mitotic catastrophe caused by telomere shortening. Replication of somatic cells, which do not express telomerase, leads to shortened telomeres. In the presence of competent checkpoints, cells undergo arrest and enter non replicative senescence. In the absence of checkpoints, DNA repair pathways, such as the non homologous end-joining (NHEJ) pathway are inappropriately activated, leading to the formation of dicentric chromosomes. At mitosis the dicentric chromosomes are pulled apart, generating random double-stranded breaks, which then activate DNA-

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repair pathways, leading to the random association of double-stranded ends and the formation, again, of dicentric chromosomes. Cells undergo numerous rounds of this bridge-fusion-breakage cycle, which generates massive chromosomal instability and numerous mutations. If cells fail to reexpress telomerase, they eventually undergo mitotic catastrophe and death. Reexpression of telomerase allows the cells to escape the bridge-fusion-breakage cycle, thus promoting their survival and tumorigenesis.

Angiogenesis

Even if a solid tumor possesses all of the genetic aberrations that are required for malignant transformation, it cannot enlarge beyond 1 to 2 mm in diameter unless it has the capacity to induce angiogenesis

The current paradigm is that angiogenesis is controlled by a balance between angiogenesis promoters and inhibitors; in angiogenic tumors this balance is skewed in favor of promoters.

Hypoxia triggers angiogenesis through the actions of HIF-1a on the transcription of the proangiogenic factor VEGF.

Many other factors regulate angiogenesis; for example, p53 induces synthesis of the angiogenesis inhibitorthombospondin-1, while RAS, MYC, and MAPK signaling all up regulate VEGF expression and stimulate angiogenesis.

VEGF inhibitors are used to treat a number of advanced cancers and prolong the clinical course, but are not curative

### Invasion and Metastasis

Invasion of the ECM initiates the metastatic cascade and is an active process that can be resolved into several steps:

- "Loosening up" of tumor cell-tumor cell interactions
- Degradation of ECM
- Attachment to novel ECM components
- Migration and invasion of tumor cells

A. Loosing of Intercellular Junction

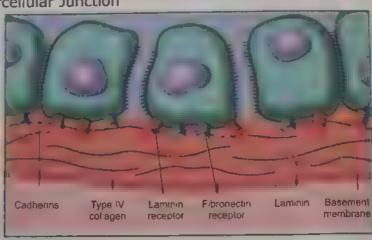


Fig. 4.20:



B. Degradation of ECM

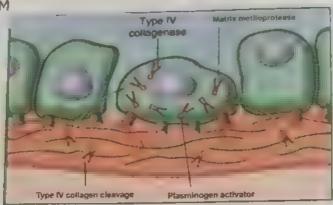


Fig. 4.21:

C. Migration and Invasion

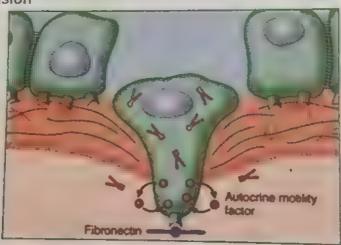


Fig. 4.22:

Dissociation of cancer cells from one another is often the result of alterations in intercellular adhesion molecules and is the first step in the process of invasion

- The metastatic site of many tumors can be predicted by the location of the primary tumor. Many tumors arrest in the first capillary bed they encounter (lung and liver, most commonly).
- Some tumors show organ tropism, probably due to expression of adhesion or chemokine receptors whose ligands are expressed by endothelial cells the metastatic site.
- Genes that promote epithelial-mesenchymal transitions, like TWIST and SNAIL, may be important metastasis genes in epithelial tumors

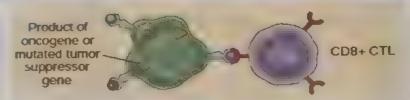
Normal host displaying multiple MHCassociated self antigens



Examples

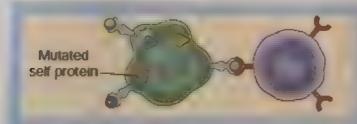
Iumor cells expressing different types of tumor antigens

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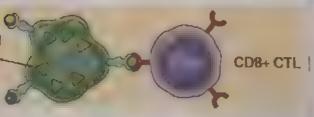
Oncogene products: mutated RAS, BCR/ABL fusion proteins

Tumor suppressor gene products: mutated p53 protein



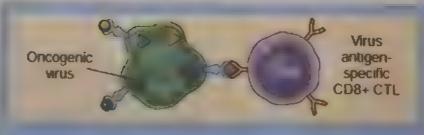
Various mutant proteins in carcinogen, or radition, induced animal tumors; various mutated proteins in melanomas

Overexpressed or aberrantly \_ expressed self protein



Overexpressed: tyrosinase, gp 100, MART in melanomas

Aberrantly expressed: cancertestis antigens (MAGE, BAGE)



Human papilloma virus F6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphoma

Fig. 4.23:

### Mechanisms by Which Tumors Evade The Immune System.

Tumors may evade immune responses by losing expression of antigens or major histocompatibility complex (MHC) molecules or by producing immune-suppressive cytokines or ligands such as PD-L1 for inhibitory receptors on T cells.

### Genomic Instability as Enabler of Malignancy

- Persons with inherited mutations of genes involved in DNA repair systems are at greatly increased risk for the development of cancer.
- Patients with HNPCC syndrome have defects in the mismatch repair system, leading to development of carcinomas of the colon. These patients' genomes show microsatellite instability, characterized by changes in length of short repeats throughout the genome.

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- Patients with xeroderma pigmentosum have a defect in the nucleotide excision repair pathway and are at increased risk for the development of cancers of the skin exposed to UV light, because of an inability to repair pyrimidine dimers.
- . Syndromes involving defects in the homologous recombination DNA repair system constitute a group of disorders-Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia-that are characterized by hypersensitivity to DNA damaging agents, such as ionizing radiation. BRCA1 and BRCA2, which are mutated in familial breast cancers, are involved in DNA repair.
- . Mutations incurred in lymphoid cells due to expression of gene products that induce genomic instability (RAG1, RAG2, AID) are important causes of lymphoid neoplasms.

# Genetic Lesions in Cancer

- . Tumor cells may acquire several types of oncogenic mutations, including point mutations and other nonrandom chromosomal abnormalities, such as translocations, deletions, and gene amplifications.
- Balanced translocations contribute to carcinogenesis by overexpression of oncogenes or generation of novel fusion proteins with altered signaling capacity. Deletions frequently cause loss of tumor suppressor gene function, and occasionally activate proto-oncogenes. Gene amplification
- Generally increases the expression and function of oncogenes.
- Genomic sequencing has revealed numerous "cryptic" (sub cytogenetic) rearrangements, mainly small deletions and insertions ("indels"), as well as chromothrypsis, in which a chromosome is "shattered" and then reassembled in a haphazard way.

chromosome is "shattered"	Tpanslocalina	Affectact Cenes
Chronic myelogenous leukemia	(9:22) (q34; q11)	ABL 9q34 BCR 22q11
Ate myeloid leukemia (AML)	(8,21) (q22; q22) (15;17)(q22;q21)	AML 8422 ETO 21422 PML 15422 • RARA 17421
Barkitt lymphoma	(8.14)(q24;q32)	MYC 8q24 IGH 14q32
Mantle cell lymphoma	(11,14)(q13,q32)	CCND1 11q13 1GH 14q32
Follicular lymphoma	(14;18)(q32;q21)	IGH 14q32 BCL2 18q21
Ewing sarcoma	(11;22)(q24;q12)	FL11 11q24 
Prostatic adenocarcinoma	(7:21) (p22; q22) (17:21) (p21; q22)	TMPRSS2 (21q22.3) ETV1 (7p21.2) ETV4 (17q21)

		I make the same
	DNA methylation	Acute myeloid leukemia (20%)
DNMT3A	III stone methy lation	Acute leukemia in Infants (90%
MLLI	HI stone methylation	Follicular lymphoma (90%)
MLL2 CREBBP/ EP300	HI stone acety lation	Diffuse large B cell lymphoma (40%)
ARID 1A	Nucleosome positioning/chromatin remodeling	Ovarian clear cell carcinoma (60%), endometrial carcinoma (30%-40%)
SNF5	Nucleosome positioning/chromatin remodeling	Malignant rhabdoid tumor (100%)
PBRM1	Nucleosome  Positioning/chromatin remodeling	Renal carcinoma (30%)

### **Chemical Carcinogenesis**

- Chemical carcinogens have highly reactive electrophile groups that directly damage DNA, leading to mutations and eventually cancer.
- Direct-acting agents do not require metabolic conversion to become carcinogenic, while indirect-acting agents are not active until converted to an ultimate carcinogen by endogenous metabolic pathways. Hence, polymorphisms of endogenous enzymes such as cytochrome P-450 may influence carcinogenesis.
- After exposure of a cell to a mutagen or an initiator, tumorigenesis can be enhanced by exposure to promoters, which stimulate proliferation of the mutated cells.
- Examples of human carcinogens are direct-acting agents (e.g., alkylating agents used for chemotherapy), indirect acting agents (e.g., benzo[a]pyrene, azo dyes, aflatoxin), and promoters or agents that cause pathologic hyperplasias of the endometrium or regenerative activity in the liver.

The UV portion of the solar spectrum can be divided into three wavelength ranges: UVA (320-400 nm), UVB (280-320 nm), and UVC (200-280 nm). Of these, UVB is believed to be responsible for the induction of cutaneous cancers. UVC, although a potent mutagen, is not considered significant because it is filtered out by the ozone layer surrounding the earth (hence the concern about ozone depletion).

## Viral and Bacterial Oncogenesis

HTLV-1: a retrovirus that is endemic in Japan, the Caribbean, and parts of South America and Africa that causes adult T-cell leukemia/lymphoma

- HTLV-1 encodes the viral protein Tax, which turns on pro-growth and pro-survival signaling pathways (PI3K/AKT, NF-kB), leading to a polyclonal expansion of T cells.
- After a long latent period (decades), a small fraction of HTLV-1-infected individuals develop adult T-cell leukemia/lymphoma, a CD4+ tumor that arises from an HTLV-1-infected cell, presumably due to acquisition of additional mutations in the host cell genome.



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HPV: an important cause of benign warts, cervical cancer, and oropharyngeal cancer

- Oncogenic types of HPV encode two viral oncoproteins, E6 and E7 that bind to Rb and p53, respectively, with high affinity and neutralize their function.
- Development of cancer is associated with integration of HPV into the host genome and additional mutations needed for acquisition of cancer hallmarks.
- . HPV cancers can be prevented by vaccination against high-risk HPV types.

EBV: ubiquitous herpes virus implicated in the pathogenesis of Burkitt lymphomas, B-cell lymphomas in patients with T-cell immunosuppression (HIV infection, transplant recipients), and several other cancers

- . The EBV genome harbors several genes encoding proteins that trigger B cell signaling pathways; in concert, these signals are potent inducers of B cell growth and transformation.
- In the absence of T-cell immunity, EBV-infected B cells can rapidly "grow out" as aggressive B-cell tumors.
- In the presence of normal T-cell immunity, a small fraction of infected patients develop EBV-positive B-cell tumors (Burkitt lymphoma, Hodgkin lymphoma) or carcinomas (nasopharyngeal, gastric carcinoma)

Hepatitis B virus and hepatitis C virus: cause of between 70% and 85% of hepatocellular carcinomas worldwide

- Oncogenic effects are multifactorial; dominant effect seems to be immunologically mediated chronic inflammation, hepatocellular injury, and reparative hepatocyte proliferation.
- HBx protein of HBV and the HCV core protein can activate signal transduction pathways that also may contribute to carcinogenesis.

H. pylori: implicated in gastric adenocarcinoma and MALT lymphoma

- Pathogenesis of H. pylori-induced gastric cancers is multifactorial, including chronic inflammation and reparative gastric cell proliferation.
- · H. pylori pathogenicity genes, such as CagA, also may contribute by stimulating growth factor pathways.
- Chronic H. pylori infection leads to polyclonal B-cell proliferations that may give rise to a monoclonal B-cell tumor (MALT lymphoma) of the stomach as a result of accumulation of mutations.

### Paraneoplastic Syndromes:

Hypercalcemiais probably the most common paraneoplastic syndrome; in fact, symptomatic hypercalcemia is more often related to some form of cancer than to hyperparathyroidism.

Two general processes are involved in cancer-associated hypercalcemia:

- 1. osteolysis induced by cancer, whether primary in bone, such as multiple myeloma, or metastatic to bone from any primary lesion, and
- 2. the production of calcemic humoral substances by extra osseous neoplasms.

Only the second mechanism is considered to be paraneoplastic; hypercalcemia due to primary or secondary involvement of the skeleton by tumor is not a paraneoplastic syndrome

Syndrome of inappropriate antidiuretic hormone secretion

Cushing syndrome

Hypercalcemia

Hypoglycemia

Polycythemia

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	Small-cell carcinoma of lung pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
	Small-cell carcinoma of lung intracranial neoplasms	Antidiuretic hormone or a r natriuretic hormones
1	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T-cell leukemia/lymphoma	Parathyroid hormone-related protein (PTHRP), TGF-a, TNF

Erythropoietin

Insulin or insulin-like substate.

There and Muselowadional				
Myasthenia	Bronchogenic carcinoma  Thymic neoplasms	Immunologic		
Disorder of the central and peripheral nervous system	Breast carcinoma			
Dermatologic Disorders				
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor		
Dermatomyositis	Bronchogenic carcinoma Breast carcinoma	Immunologic		

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Ovarian carcinoma

Other mesenchymal sarcomas

Fibrosarcoma

Renal carcinoma

Cerebellar hemangioma Hepatocellular carcinoma atria!

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### Osseons, Articular, and Soft Thone Change

Hypertrophic osteoarthropathy and ubbing of the fingers

Bronchogenic carcinoma Thymic neoplasms

Unknown

Vascular and Hematologic Changes

venous thrombosis (Trousseau phenomenon)

Pancreatic carcinoma Bronchogenic carcinoma

Tumor products (mucins that activate clotting)

Disseminated intravascular

coagulation

Other cancers Acute promyelocytic leukemia

Tumor products that activate clotting

Nonbacterial thrombotic

endocarditis Red ce.l aplasia

Hypercoagulability Advanced cancers

Thymic neoplasms

Prostatic carcinoma

Unknown

Others

Nephrotic syndrome

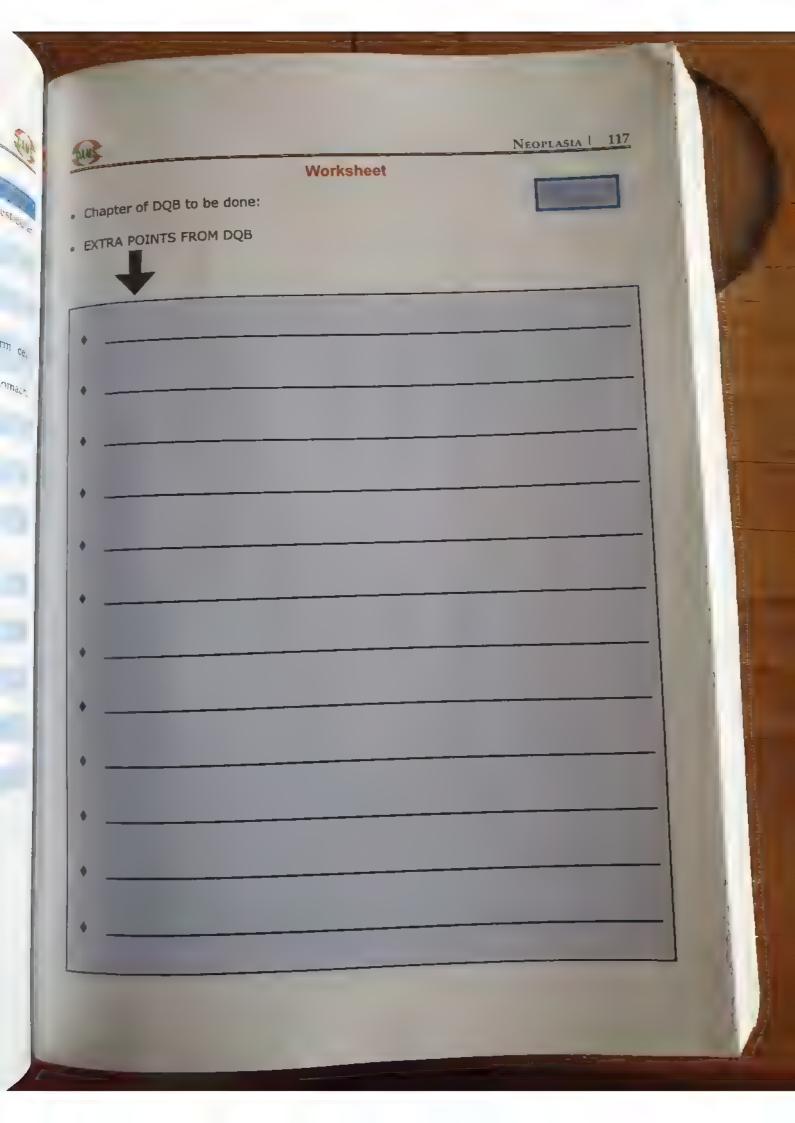
Various cancers Tumor antigens, immune complexes

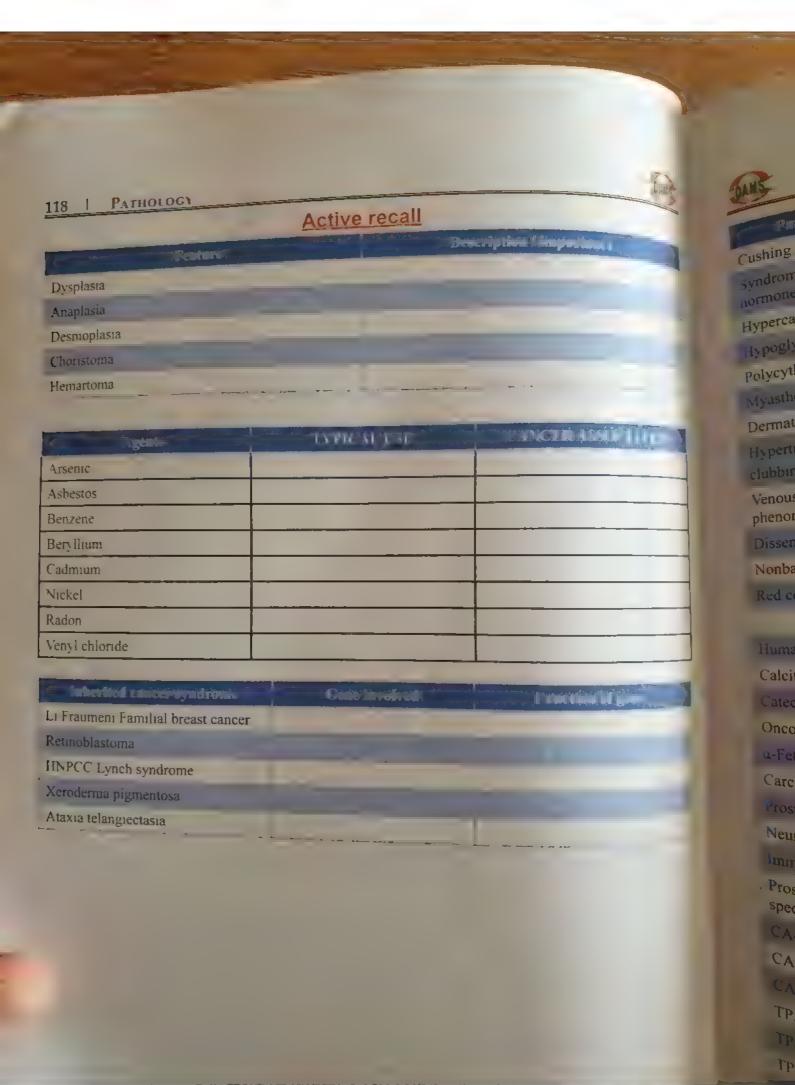
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# **Tumor Markers**

Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	
Oncofetal Antigens	
a-Fetoprotein	Liver cell cancer, non seminomatous germ cell tumors of testis
Carcinembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
Isoenzymes	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small-cell cancer of lung, neuroblastoma
Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen and prostate-specific membrane antigen	Prostate cancer
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer
Cell-Free DNA Markers	
TP53, APC, RAS mutants in stool and serum	Colon cancer
TP53, RAS mutants in stool and serum	Pancreatic cancer
TP53, RAS mutants in sputum and serum	Lung cancer
TP53 mutants in urine	Bladder cancer

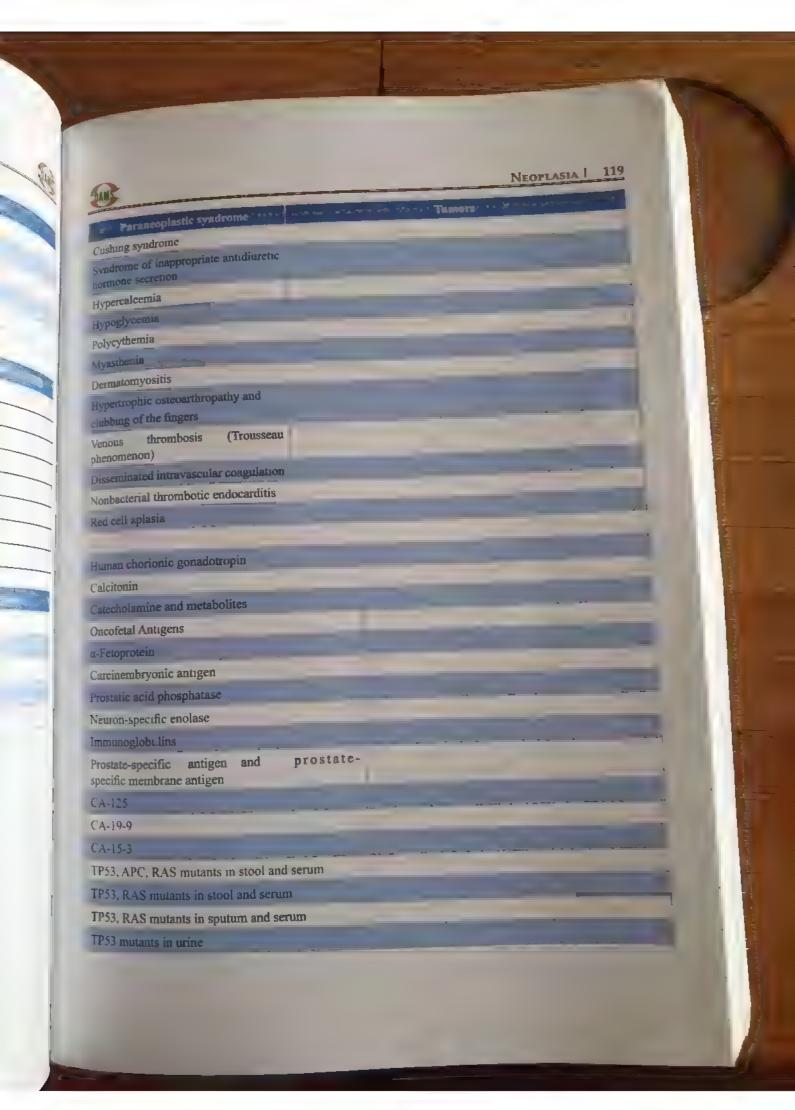




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# DISORDERS OF IMMUNE SYSTEM

# CONCEPTS

Concept 5.1: Disorders of Immune System



# Concept: Disorders of Immune System

Learning Objectives: Hypersensitivity reactions, Graft rejections, GVHD, Immunodeficiency disorders, amyloidosis

### Time Needed

1st reading	2 hours
2 <sup>nd</sup> reading	45 mins

### Introduction to Immunity

- Immunity is a systemic response to stimulus (usually antigenic).
- Two types of immunity are there Innate and acquired
- Innate immunity can occur without antigenic sensitization, usually is from birth and lacks antigenic memory
- While acquired immunity occurs after antigenic sensitization only. This will have an
  antigenic memory and usually is acquired later in life

### **Hypersensitivity Reactions**

Type of Hypersensitivity	Pathologic immune Viechanisms	
Immediate: type 1	IgE antibody, TH2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody-mediated: type 2	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement-and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular function, e.g., hormone receptor signaling. neurotransmitter receptor blockage
Imbue complex-mediated: Type 3	Imbue complexes of circulating antigens and IgM or IgG antibodies	Complement-and Fc receptor—mediated recruitment and activation of leukocytes
T cell-mediated type 4	CD4+T cells (TH 1 and TH17 cells) CD8+ CTLs	Cytokine-medicated inflammation  Direct target cell killing, cytokine- medicated inflation

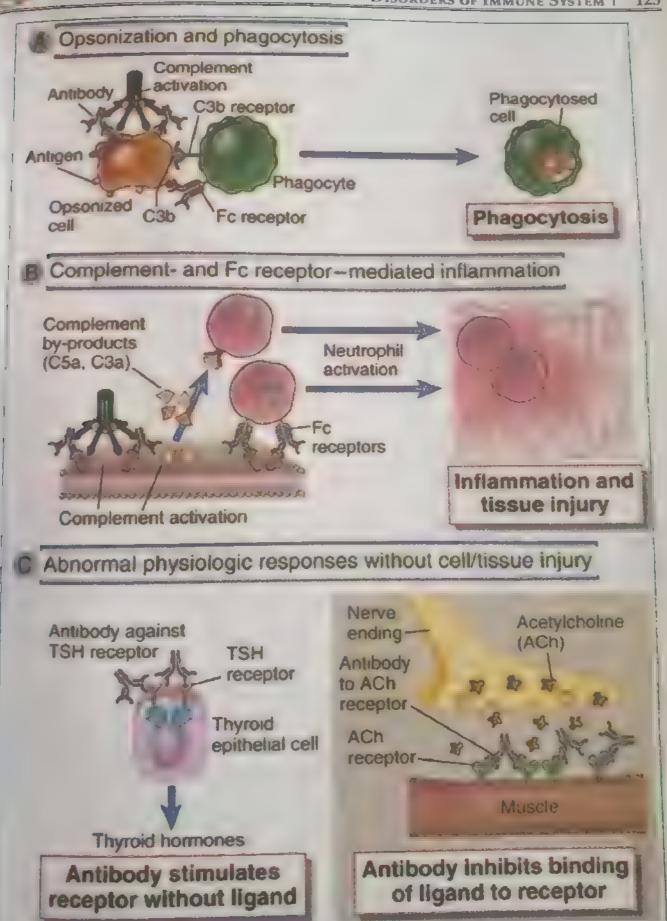


Fig. 5.1:

Neutrophila

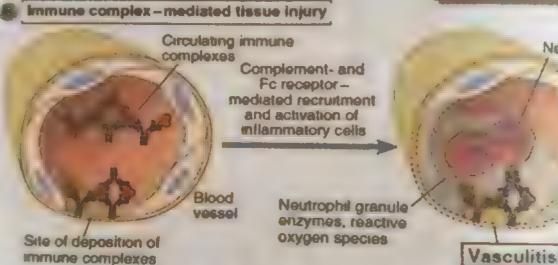


Fig. 5.2:

## Type I Hypersensitivity Reaction

Anaphylaxis: Prior sensitization has resulted in an immune response initially mediated by CD4 lymphocytes (of the Th2 variety) that promote mast cell proliferation and plasma cell production of IgE. The IgE becomes bound to mast cells in places such as respiratory tract mucosa. Encountering the allergen again leads to mast cell degranulation with release of primary mediators (such as histamine, serotonin) which cause vasodilation, bronchoconstriction, etc. and release of secondary mediators (such as leukotrienes, prostaglandin) which lead to inflammatory cell infiltrates.

### **Laboratory Findings**

- Type 1 hypersensitivity reactions may be accompanied by an increase in eosinophils, as noted with differential count of peripheral white blood cells.
- The serum tryptase may be increased in the hour following mast cell activation.

Measurement of serum total IgE and levels of specific IgE for certain antigens may be undertaken when allergy therap es are planned. Testing for total or specific IgE be undertaken when the history is consistent with allergy and specific allergens should be done only when the history is consistent with allergy and specific allergens are suspected as the cause.

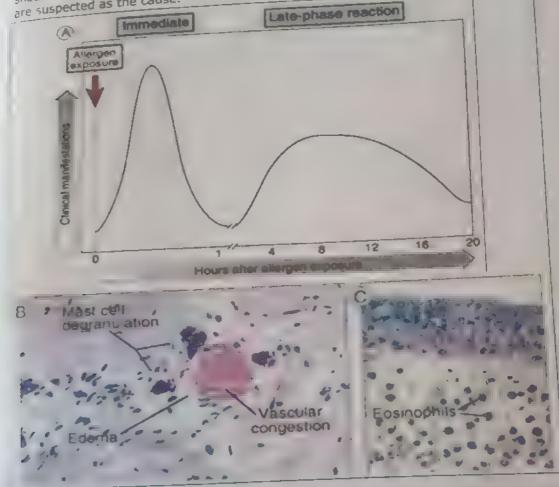


Fig. 5.3. Phases of immediate hypersensitivity reactions. A, Kinetics of the immediate and late-phase reactions. The immediate vascular and smooth muscle reaction to allergen develops within minutes after challenge. (Allergen exposure in a previously sensitized individual) and the late-phase reaction develops 2 to 24 hours later. The immediate reaction (B) is characterized by vasodilation, congestion, and edema, and the late-phase reaction (C) is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells. (Courtesy Dr. Daniel Friend, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

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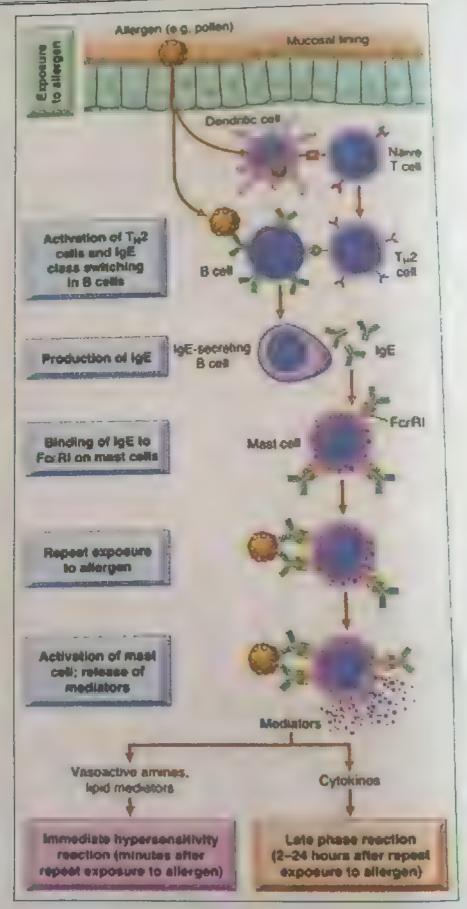


Fig. 5.4:

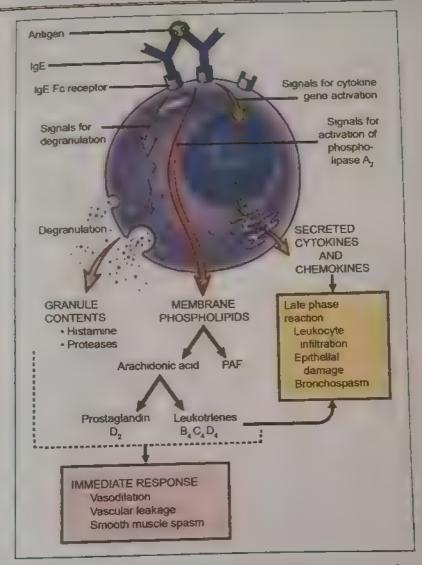


Fig. 5.5: Mast cell mediators. Upon activation, mast cells release various classes of mediators that are responsible for the immediate and late-phase reactions. PAF, Platelet activating factor.

Clinical Syndrome	Chargal and paynoings: Manifestations	
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) cause by vascular dilation; airw obstruction due to laryngeal edema	
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity, inflammation and tissue injury caused by late-phase reaction	
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; Inflammation of upper airways, smuses	
Pood allergies	Increased peristalsis due to contraction of intestinal muscles	

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# Type II Hypersensitivity Reaction

Complement dependent reactions: Antibody is directed against antigen on cells (such as circulating red blood cells) or extracellular materials (basement membrane). The resulting Ag-Ab complexes activate complement (via the classic pathway), leading to cell lysis or extracellular tissue damage.

Antibody-dependent cell-mediated cytotoxicity (ADCC): Low concentrations of IgG or IgE (in the case of parasites) coat target cells. Inflammatory cells such as NK (natural killer) cells, monocytes, and granulocytes then bind to the immunoglobulin Fc receptors and lyse, but do not phagocytize, the target cells.

Antireceptor antibodies: IgG antibody is directed against receptors in target cells, resulting in complement-mediated destruction of the receptors.

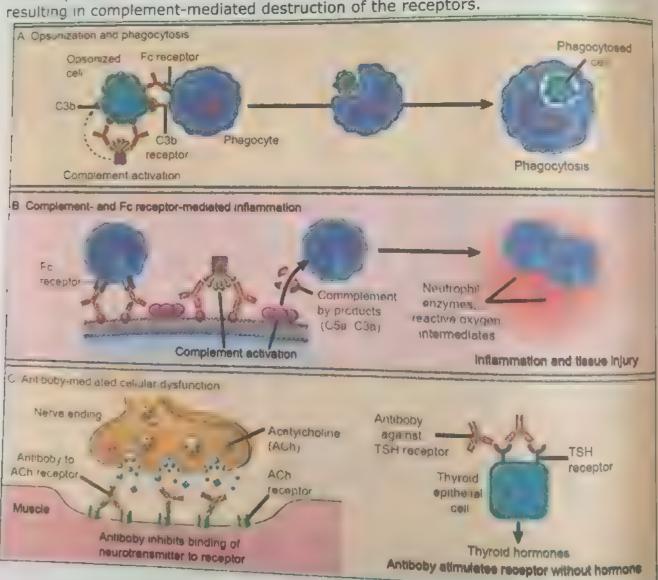


Fig. 5.8:

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Autoimmune hemolytic	Red cell membrane proteins (Mi blood group antigens 1 antigen)	Opsonization and phagocytosis of red cells	Hemolysis, anemia
A Holmmune broinbocytopenic	Platelet membrane proteins (Gpllb illa integrin)	Opsonization and phagocytosis of platelets	Bleeding
pemphigus vulgaris	Proteins in Intercellular Junctions of epidermal cells	Antibody-mediated activation of proteases, disruption of Intercellular adhesions	Skin vesicles (bullae)
Vasculius caused by	Neutrophil granule contents, presumably released from activated neutrophils	Neutrophil degeneration and Inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein In basement membranes of Kıdney glomeruli and lung alveoli	Complement- and Fc receptor-mediated Inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody Inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism!	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insult-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosts
Pernicious anemia	Intrinsic factor of gastro parietal cells	Neutralization of Intrinsic factor, decreased absorption of vitamin B1z	Abnormal erythropotesis, anem of
		Vitamin D12	

# Type III Hypersensitivity Reaction

This reaction is mediated by immune (Ag-Ab) complexes which promote tissue damage primarily through complement activation (alternate pathway). C3b as an opsonin attracts neutrophils, which then release lysosomal enzymes. C5a as a chemoattractant brings in neutrophils. Serum complement is reduced as it is used up in this process.

# Immune complexes can be deposited systemically or locally

complex immune Systemic disease: Ag-Ab complexes form in the circulatory system and are deposited in tissues, typically near basement membranes in places such as blood vessels, glomeruli, skin, joints, pleura, pericardium. Larger and immune complexes are quickly phagocytized by macrophages and removed, but small to intermediate complexes formed with antigen excess may escape removal leading to:

- Glomerulonephritis
- Serum sickness
- Vasculitis

Local immune complex disease: Also called an "Arthus" reaction, it occurs with local injection of the antigen and leads to focal vasculitis. This kind of immune reaction also plays a role in the development of hypersensitivity pneumonitis (so-called "farmer's lung").

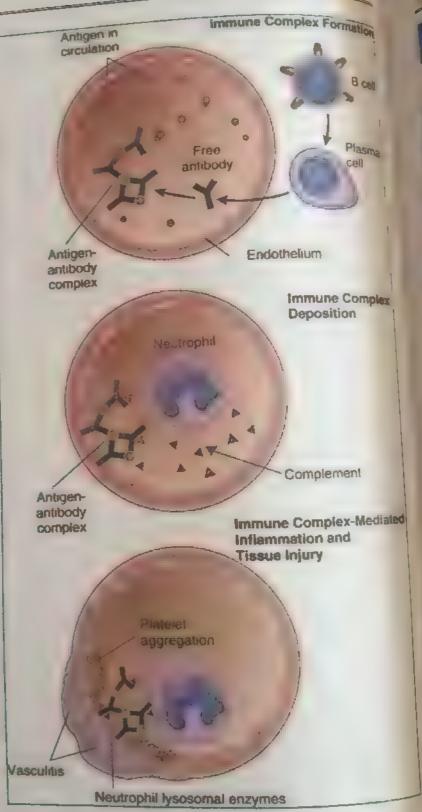


Fig. 5.7: Immune complex disease The sequential phases in the induction of systemic immune complex-mediated diseases (type III hypersensitivity).

Systemic lu ervihemato

post strepti

Reactive : Serum sic

Arthus re

Type I

Fig.

Th

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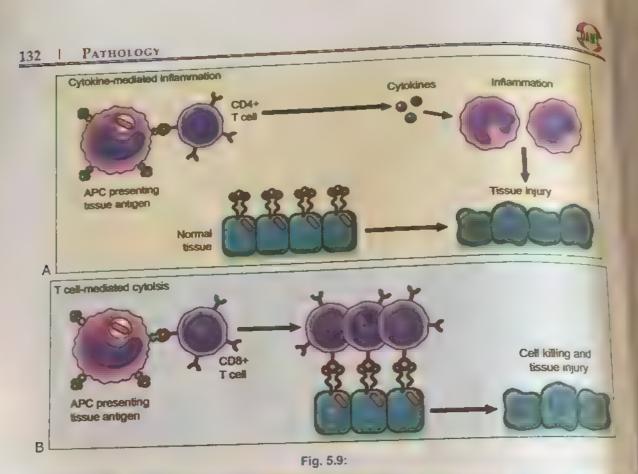
Ch. Charles	) etter efficientions	Charles and the Control of the Contr
Systemic lupus erythematosus	Nuclear antigens (circulating or "planted" In kidney)	Nephritis, skin lesions.
Post streptococeal glomerulonephritis	Streptococcal cell wall antigen(s); maybe "planted" In glomerular basement membrane	Nephritis
Polyarteritis nodosa	Hepatitis B virus antigens In some cases	Systemic vasculitis
Reactive arthritis	Bacterial antigens (e.g., Yersinia)	Acute arthrus
Serum sickness	Various proteins, e.g., foreign serum protein (horse antithymocyte globulin!	Arthritis, vasculitis, nephritis
Arthus reaction experimental!	Various foreign proteins	Cutaneous vasculitis

piplet

Type IV Hypersensitivity Reaction THI COL Activated macrophage Giant cell Monocytes Fibroblast: Blood Lymphocyte vessel

Fig 5.8 Granulomatous inflammation A, Lymph node from a patient with tuberculosis containing granulomas with activated macrophages, multinucleate giant cells, and lymphocytes. In some granulomas, there may be a central area of necrosis. Immunohistochemmical studies would identify the Lymphocytes as T cells B. Mechanisms of granuloma formation. Cytokines are involved in the generation of T<sub>H</sub>1 cells, activation of macrophages and recruitment of leukocytes. Prolonged reactions of the type lead to the formation of granulomas.

This reaction is called "delayed hypersensitivity" because it is mediated by sensitized CD4+ T lymphocytes which process antigens in association with class II HLA molecules and release lymphokines. The lymphokines promote a reaction (especially mediated through macrophages) beginning in hours but reaching a peak in 2 to 3 days.



Examples of the T cells a

Amyloidos

pathologi

organs A progressive physical n Non bra

Diamete

X-ray crys

Charact

Principal Vicenauisms of y of Fathegenic disme bijury F cells Inflammation mediated Chronic arthritis with Collagen? Cirtullinated self-Rheumatoid inflammation, destruction of by TH 17 (and T H1?) proteins? arthritis articular cartilage cytokines; role of antibiotics and immune complexes? Demyelination in CNS with Protein antigens in myelin Inflammation medicated by Multiple perivascular Inflammation, (e g., myelin basic protein) TH1 and TH17 cytokines, Sclerosis myelin destruction by paralysis, activated macrophages T cell-medicated Insulitis (chormic Type 1 Antigens of pancreatic islet inflammation, in islet) inflammation, destruction diabetes B cells (Insulin, glutamic destruction of B cells; diabetes acid decarboxylase, Other) of islet cells by CTLs Mellitus Chronic intestinal Inflammatory Enteric bacteria: self-Inflammation mediated by inflammation, obstruction antigens? bowel TH1 and TH17 cytokines diseases Destructive plaques in the Unknown Inflammation mediated **Psoriasis** mainly by TH17 cytokines skin Epidermal necrosis, dermal Various environmental Inflammation mediated Contact inflammation, causing skin chemicals (e.g., urushiol from by TH1(and TH17?) sensitivity

cytokines

rash and blisters

poison ivy or poison oak)

Examples of human T cell-mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue Injury.

Pathologic proteinaceous substance, deposited between cells in various tissues and organs Amorphous, Eosinophilic, Hyaline, extracellular substance

 $p_{rogressive}$  accumulation  $\rightarrow$  pressure atrophy of adjacent cells

# **Physical nature of Amyloid**

- Non branching fibrils of indefinite length
- . Diameter: 7.5 -10 nm.

# X-ray crystallography and Infra red spectroscopy

• Characteristic cross  $\beta$  – pleated sheet confirmation. (responsible for birefringence)

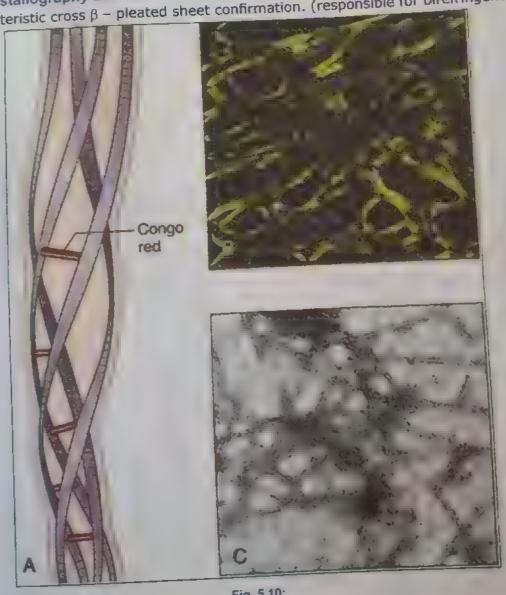


Fig. 5.10:

Structure of amyloid. A, an amyloid fiber schematically showing four fibrils (there can be as many as six in each fiber) wound around one another with regularly spaced binding of the Congo red dye. B, Congo red staining shows apple-green birefringence under polarized light, a diagnostic feature of amyloid. C, Electron micrograph of 7.5-to 10-nm amyloid fibrils

# 15 biochemically distinct forms

3 more common forms:

- a. AL (amyloid light chain)
- derived from plasma cells (most AL-LAMBDA VI)
- Contains Ig light chains
- b. AA (Amyloid associated) Non - immunoglobulin protein synthesized by liver
- c. Aß amyloid: In cerebral lesion of Alzheimer disease

Classification of Amyloidosis:

lassification of Amyloi	dosis:		The same of the Holes of
Clinicopathologic Category	Associated Diseases	Ma <sub>l</sub> or Fibril Protein	Chemically Related Precursor Protein
Systemic (Generalized) Amyloid	dosis		
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal plasma cell proliferations	AL	Immunoglobulin light chains, chiefly λ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	Aβ2m	β2-microglobulm
Hereditary Amyloidosis			
Familial Mediterranean fever		AA	SAA
Familial amyloidotic neuropathies (several types)		ATTR	Transthyretin
Systemic Senile Amyloidosis	*	ATTR	Transthyretin
Localized Amyloidosis			
Senile cerebral	Alzheimer disease	Ab	APP
Endocrine		A Cal	Calcitonin
Medullary carcinoma of thyroid	Type 2 diabetes	Alapp	Islet amy loid peptide
Islets of Langerhans		AANF	Atrial natriuretic factor
Isolated atrial amyloidosis			

A. 545 B. LOC

A. 5Y 1. PRI AL:

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2. RE . Al

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### Types:

A. SYSTEMIC

B. LOCALIZED

A. SYSTEMIC 1. PRIMARY AMYLOIDOSIS / Immunocyte dyscrasias: systemic amyloidosis

AL: Complete Ig light chain - NH, terminal fragment both

Most common - Lambda or kappa

- Associated with plasma cell dyscrasia
- Systemic in nature

5-15% of pts, With Multiple Myeloma develop AL Amyloidosis

- 2. Reactive Systemic Amyloidosis / Secondary Amyloidosis
- AA protein deposited
- Secondary to associated inflammations
- Systemic disorder

### Association:

Prev: TB, bronchiectasis, chronic osteomyelitis

Now, most common: Rheumatoid Arthritis (13% of pts. Dev. AA)

Ankylosing spondylitis

Inflammatory bowel disease

Others: Heroine abuses

RCC

Hodgkin's disease

Chronic inflammation → Macrophages Activation → IL-1 & IL-6 → Liver cells

SAA Protein **Limited Proteolysis** 

AA Protein

# 3. Hemodialysis associated amyloidosis:

- Deposition of β<sub>2</sub> Microglobulin (component of MHC class I molecule) (Can't be filtered through cuprophane dialysis membranes)
- Deposits is synovium, joints & tendon sheaths

### 4. Heredofamilial Amyloidosis

- a. Familial Mediterranean fever: Fever with inflammation of serosal surface (Pleura, peritoneum & synovial membrane)
  - Deposits of AA proteins
  - \*AR Gene product → 'Pyrin': Exact function not known? Regulates acute inflammations

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# b. Familial amyloidotic neuropathies (several types):

- Both peripheral & autonomic nerves involved
- AD
- Deposits of ATTR (Trans thyretin) (Mutant form)

## c. Systemic senile Amyloidosis

- Deposits of ATTR (structurally normal)
- Deposits in heart of aged individuals (70-80 years)
- b. LOCALIZED AMYLOIDOSIS: Nodular deposits most often in lung, larynx, skn, urinary bladder, tongue around etc.
- 1. Senile cerebral amyloidosis
  - Found in Alzheimer's disease

Deposits:  $-\beta$  – amyloid protein (A $\beta$ ) Precursor: Amyloid precursor protein

### 2. Endocrine

- a. Medullary carcinoma of thyroid
  - Deposits of A cal

(Precursor: calcitonin)

- b. Islet of Langerhans (in Type II DMA)
  - Deposits: AIAPP

(Precursor: Islet Amyloid Peptide)

c. Isolated Atrial Amyloidosis: Deposits: AANF

(Precursor- Atrial Natriuretic factor)

d. Prion Disease - Mis folded Prion protein

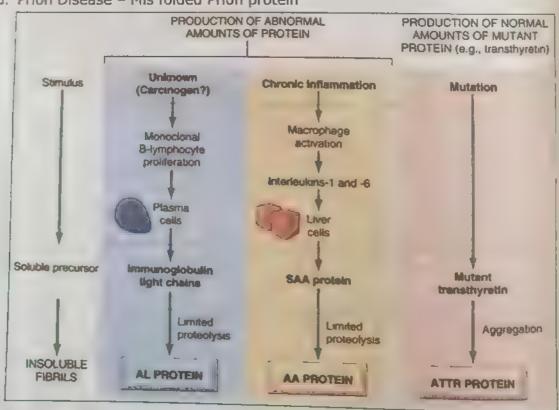


Fig. 5.11:

Morphol AA: M. S AL: Hea

Gross: Cut Surf

Staining

2. Cong polariz

3. Crys

4. Thio

5. Imn

6. Elec

101000

Splee

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Morphology: AA: M. severe systemic involvement · Kidneys, Liver, Spleen, Lymph nodes, Adrenal, Thyroid

AL: Heart, kidney, GIT, Peripheral nerves, Skin, Tongue

Gross: Organ → enlarged, firm, waxy

Cut surface paint with H2SO4

yellow color →

→Iodine ---- Blue violet Colour

### Staining:

GIT

λη<sub>χ</sub> ς,

1. PAS+ (: of P component → glycoproteins)

2 Congo red -- on light Microscopy it appears Light pink

Polarized Light ---- Green Birefringence

After t/t with KMnO<sub>4</sub> AA protein losses its affinity

3. Crystal violet/ methyl violet

4. Thioflavin 'T & S'

5. Immunohistochemical staining

6 Electron Microscopy

Most common and most serious form of organ involvement Kidney In interstitial peritubular tissue, arteries & arterioles

Sago spleen: In splenic follicles Sp.een On gross: tapioca like granules

Lardaceous spleen: In walls of splenic sinuses & in red pulp

Large, map like areas

First in space of Disse Liver - pressure atrophy

Also vascular involvement & Kupffer cell deposition

Focal subendocardial accumulation and between the muscle fibres Heart (May damage conduction = ECG abnormalities)

May present as CHF, arrhythmias

Initially in Zona glomerulosa Adrenals

> Any level: Gingiva to anus Tongue = macroglossia

Tumor forming amyloid of the tongue

Most common organ involved in amyloidosis- Kidney

Most common cause of mortality in primary amyloidosis- cardiac

Most common cause of mortality in secondary amyloidosis- renal

Most common cause of mortality overall- cardiac

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Prognosis: Poor for generalized amyloidosis

AL (not including MM) → median 2 years survival.

In MM → Worse Prognosis

AA → Control the cause → Better Prognosis

# **Transplant Rejection**

Graft rejection depends on recognition of grafted tissue as foreign by host.

In

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HYF

\_ ic M/E

- Both cellular and humoral immunity play a role.
- Hypersensitivity type II, III, IV involved.

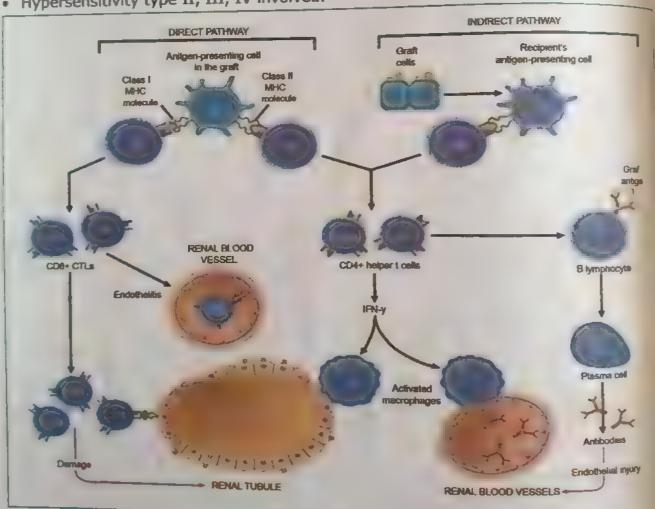


Fig. 5.12:



- 1. Hyperacute- Mediated by preformed antidonor antibodies
- . Within minutes or hours after transplantation
- Initial target- Graft vasculature
- . Type II HR at the level of vascular endothelium.
- Commonly seen in patients who have received multiple blood transfusion / transplant before

Morphology

Hyperacute: Gross- cyanotic mottled, flaccid organ within minutes of joining vasculature - identified by surgeon himself- earliest feature of rejection

M/E - Neutrophilic vasculitis with thrombosis

- 2. A. Acute Cellular rejection Most common type of graft rejection seen within few days to months or after removal of immunosuppressive drag.
- Interstitial inflammatory infiltrate (CD4, CD8)
- Glomerular and peritubular capillaries, show large number of mononuclear cells
- Tubulitis is most characteristic feature of this
- After removal of immunosuppressive drugs.
- Most frequent form of rejection
- Responds to immuno suppressive therapy.
- Type IV HR

### 2. B. Acute humoral rejection

- Necrotizing vasculitis, intimal thickening of arteries.
- Endothelial necrosis
- Deposition of immunoglobulin, fibrin and thrombosis
- Responds poorly to increased doses of immuno suppression.
- 3. Chronic Rejection: Occurs when acute rejection is revolved by parenchymal fibro-SIS.
- \* Vascular changes Obliterative intimal fibrosis especially in cortical arteries
- Interstitial mononuclear infiltrate lymphocytes, plasma cells and eosinophils
- Tubular atrophy and global Glomerulosclerosis (post trans plant Glomerulo pathy)

To summarize:

Hyperacute- type II Acute humoral- type II Acute cellular – type IV

Chronic- fibrotic reaction > type IV

Transplantation of Hematopoetic organs: Three major problems in allogenic BM transplant

1. Graft versus host disease: - immunologically competent cells or precursors are transplanted into immunosuppressed host. Recipients of bone marrow transplant are immuno deficient because of primary disease or treatment. When such recipients receive normal bone marrow cells from allogenic donors, the immuno competent T cells (CD4, CD8 T cells) recognize recipients HLA antigens as foreign and attack the host tissue. Present as:



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Acute GVH - Involvement of immune system & epithelia of skin (rashes), liver (jaundice) & GIT (diarrhea) by lymphocytic infiltration.

Chronic GVH: May follow acute GVH or occurs insidiously. Severe fibrotic damage of skin, immune system GIT (oesophageal strictures), lungs, xerophthalmia and musculoskeletal system. There is involution of thymus and depletion of lymphocytes from lymph nodes. Allogenic T cells in the graft lead to GVHD but there are required for engraftment of graft and control of leukemia. This is known as graft versus leukemia

- 2. Transplant rejection: Mediated by NK cells & T cells of host.
- 3. Immunosuppressive: CMV infection is most common (lung, GIT), others- HSV, parasite and fungal infections can also occur.

### **Autoimmune Disease**

Immune reaction against self antigens.

Implies loss of immunologic tolerance (clonal deletion, clonal anergy and peripheral suppression)

### Mechanism of auto immunity-

Bypass of T helper cell tolerance
 Modification of molecule (drug induced hemolytic anemia, RA)

Molecular mimicry (Rheumatic carditis)

- 2. Polyclonal lymphocyte activation- By endotoxin or EBV. Anergic clones get stimulated
- 3. Imbalance of suppressor-helper function-Decreased supp and increased helper activity
- 4 Emergence of sequestered antigen (spermatozoa, Lens crystalline, Myelin basic protein)
- 5. Genetic factors Linkage with HLA
- 6. Microbial agents- Mechanism 1, 2, and 3

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Enviromental stimuli Genetic susceptibility Infections, tissue injury, inflammation Susceptibility - Tissue genes Activation Failure of of tissue APCs self-tolerance Influx of self-reactive lymphocytes into tissues Self-reactive lymphocytes **Activation of** self-reactive lymphocytes Tissue injury: autoimmune disease

Fig. 5.13:

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Pathogenesis of autoimmunity. Autoimmunity results from multiple factors, including Patnogenesis of autoinfilities. Autoinfility statements of autoinfility susceptibility genes that may interfere with self-tolerance and environmental triggers susceptibility genes that may interfere with self-tolerance and environmental triggers (such as infections, tissue injury, and inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage

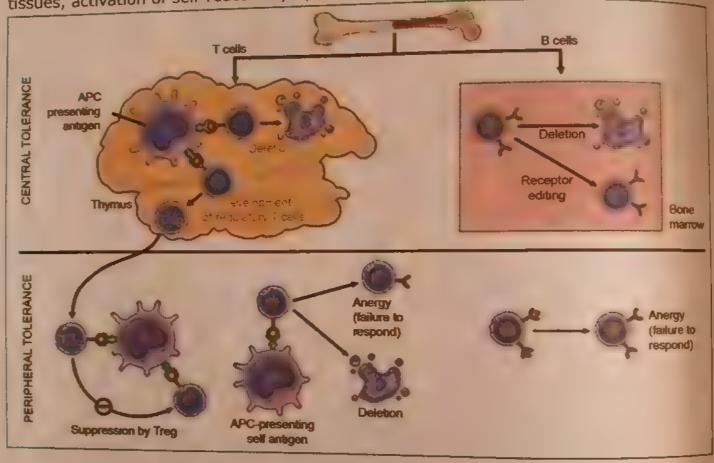


Fig. 5.14:

Mechanisms of immunologic tolerance to self antigens. The principal mechanisms of central and peripheral self-tolerance in T and B cells are illustrated



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## ntibodies in Various Autoimmune Diseases

Antinuo	lear Antibo	Disease, % Positive					
Al-marine marijen		SLE	Drug- Induced LE	Systemic Sclerosis Diffuse	Limited Scleroderma CREST	Sjogren Syndrome	Inflammatory Myopathies
Many nuclear antigens (DNA, RNA, proteins)	Generic ANA (indirect IF)	-0.5	s95	70 90	70-90	50: 80	40-60
NAI ve	Anti double- stranded DNA	40–60	<5	<5	<5	<5	<5
Histones	Ant histone	50 -70	>95	<5	<5	<5	<5
Core proteins of small nuclear RNP particles (Smith antigen)	Antı-Sm	20–30	<5	<5	<5	<5	<5
RNP (UIRNP)	Nuclear RNP	3040	<5	15	10	<5	<5
RNP	SS-A(Ro)	30-50	<5	<5	<5	70–95	10
RNP	SS-B(La)	10-15	<5	<5	<5	60–90	<5
DNA topoisom- erase I	Sel-70	<5	<5	28–70	10–18	<5	<5
Centromer- ic proteins	Anti- centromere	<5	<5	22-36	90	<5	<5
Histidyl- tRNA Synthetase	Jo-1	<5	<5	<5	<5	<5	25

ANA, antinuclear antibodies; IF, immunofluorescence; LE, lupus erythematosus; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

	Sus
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Rheumatoid arthritis (anti-CCP fit positive)  Type 1 diabetes	DRB1,1 SE allele DRB1, 2 SE alleles  DRB1*0301-DQA1*0501 -  DQB1*0201 haplotype DRB1*0401 -DQA1*0301 - DQB1*0302 haplotype
	DRB1*0301/0401 haplotype heterozygotes  DRB1 1501
Multiple sclerosis	
Systemic lupus erythematosus	DRB1*0301 DRB1*1501
Ankylosing spondylitis	B*27 (mainly B*2705 and B*2702)
Celiac disease	DQA1 *0501 -DQB1 *0201 haplotype

## Association of Non-MHC Genes with Autoimmune Diseases

- 1. Polymorphisms in a gene called PTPN22, which encodes a protein tyrosine phosphatase, are associated with rheumatoid arthritis, type 1 diabetes, and several other autoimmune diseases. Because these disorders have a fairly high prevalence (especially rheumatoid arthritis), PTPN22 is said to be the gene that is most frequently implicated in autoimmunity. It is postulated that the disease-associated variants encode a phosphatase that is functionally defective and is thus unable to fully control the activity of tyrosine kinases, which are involved in many responses of lymphocytes and other cells. The net result is excessive lymphocyte activation
- 2. Polymorphisms in the gene for NOD2 are associated with Crohn disease, a form of inflammatory bowel disease, especially in certain ethnic populations. NOD2, a member of the NOD-like receptor (NLR) family, is a cytoplasmic sensor of microbes that is expressed in intestinal epithelial and other cells. According to one hypothesis, the disease-associated variant is ineffective at sensing gut microbes, including commensal bacteria, resulting in entry of and chronic inflammatory responses against these normally well tolerated organisms
- Polymorphisms in the genes encoding the IL-2 receptor (CD25) and IL-7 receptor
  a chains are associated with multiple sclerosis and other autoimmune diseases. These
  cytokines may control the maintenance of regulatory T cells



Organ specific	Olenna	
Thyroid	Hashimoto's thyroiditis Grave's Disease	<ul> <li>Thyroglobulin</li> <li>Thyroid microsomes</li> <li>TSI, LATS</li> <li>TSH receptor Abs. Therefore,</li> <li>Action like TSH</li> </ul>
	i myxedema	TSH receptor Abs which     Block TSH action
Stomach	Chr atrophic gastritis	Gastric parietal cells
Stomach	Leads to PA	• Microsomes
		• Surface
		• F
		• IF/BI2 complex
		[Blocks interaction with B12 prevents absorption]
Adrenal cortex	Addison's disease	Adrenal cell microsomes
Adrenal cortex		leads to atrophy
		ACTH receptor
		-inhibits binding of
		ACTH to receptor
Pancreatic islet cell	Diabetic mellitus	Antibodies to Beta cells
ancicade isiet cen	Туре І	1 Insulin
Skeletal Muscle	Myasthenia gravis	Acetyl choline receptor
Preferal Ministre	111,000000	Acetylcholine binding
		Cross reactive abs to thymic
		Epithelium + Skeletal muscle

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## Immunodeficiency Diseases

Immunodence	nmunadenciencies Affecti-	J. D. Carrier
	B Cell Deficiency	T Cell Deficiency
Susceptibility to infection	Pyogeme bacteria (otitis, pneumonia, meningitis, osteomyelitis), enteric bacteria and viruses, some parasites	Pneumocystis proved, many viruses, atypical mycobacteria fungi
Diagnosis  Serum Ig levels DTH reactions to common antigens	Reduced Normal	Normal or reduced
Morphology of lymphoid tissues	Absent or reduced follicles and germinal centers (B cell zones)	Usually normal follicles, may be reduced parafollicular cortical regions (T cell zones)

DTHr delayed-type hypersensitivity.

## Examples of Infections In Immunodeficiencies

Pathozen Type	t-Celt Defect	Bell ell Denect		L D
Bacteria	Bacterial sepsis	Streptococci, staphylococci, Haemophilus	Staphylococci, Pseudomonas	Neisserial infections, other pyogenic
Viruses	Cytomegalovirus, Epstein-Barr virus, severe varicella, chronic infections with respiratory and intestinal viruses	Enteroviral encephalitis		infections
Fungi and parasites	Candida, Pneumocystis	Severe intestinal giardiasis	Candida,	
Special features	Aggressive disease with opportunistic pathogens, failure to clear infections	Recurrent sinopulmonary infections, sepsis, chronic meningitis	Nocardia, Aspergillus	



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	Congenital Disorders of Innate Is	nmunity
Disease	Functional Deficiencies	Mechanism of Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes: recurrent intracellular bacterial and fungal infections	Mutation in genes of phagocyte oxidase complex, phox 91 (cytochrome subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type I	Defective leukocyte adhesion to endothelial cells and migration into tissues linked to decreased or absent expression of p21; recurrent bacterial and fungal infections	Mutations in gene encoding the p chain (CD18) of p2 integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling and migration into tissues linked to decreased or absent expression of leukocyte ligands for endothelial E- and P-selectins, causing failure of leukocyte migration into tissues, recurrent bacterial and fungal infections	Mutations in gene encoding GDP-fucose transporter-I, required for transport of fucose into the Golgi and its incorporation into sialy! Lewis X
Leukocyte adhesion deficiency type 3	Defective leukocyte adhesion and migration into tissues linked to defective chemokine stimulated inside-out signaling and therefore defective integrin activation	Mutations in gene encoding KINDLIN-3, a cyto- skeletal protein linked to inside-out signaling
Chediak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, NK cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutation in LYST leading to defect in secretory granule exocytosis and lysosomal function
NK cell deficiencies	Reduced or absent NK cells	Mutations in the gene encoding the GATA-2 transcription factor and in the gene encoding the MCM-4 DNA helicase
Foll-like receptor agnaling defects	Recurrent infections caused by defects in TLR and CD40 signaling and defective type 1 interferon production	Mutations in TLR3, TRIF, TBK1, NEMO, UNC93B, MyD88, kBa, and IRAK-4 compromise NF-kB activate downstream of Toll-like receptors
Mendelian Susceptibility o Mycobacterial Diseases	Severe disease caused by non- tuberculous environmental mycobacteria and BCG	Mutations in IL-J2piO, IL-12RB, IENGR1, IFNGR2, STAT1, NEMO and ISG15
		ad lange 4. IVST lysosomal traffict in

BCG bacillus Calmette-Guerin; IRAK-4, IL 1 receptor-associated kinase 4; LYST lysosomal trafficking protein, NLMO, NF-ktB essential modulator.

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Disease	Functional Deficiencies	Mechanism of Defect
Defects in Cytokine Signalit	ng	
X-linked SCID	Marked decrease in T cells, normal or increased B cells, reduced serum Ig	Cytokine receptor common y chain mutations, defective T cell development in the absence of IL-7.
Autosomal recessive forms	Marked decrease in T cells; normal or increased B cells; reduced serum lg	Mutations in IL2RA, IL IRA, JAK3
Defects in Nucleotide Salva	ge Pathways	
ADA deficiency	Progressive decrease in T cells, B cells, arid NK cells; reduced serum Ig	Mutations in the ADA gene, leading to accumulation of toxic metabolites in lymphocytes
PNP deficiency	Progressive decrease in T cells, B cells, and NK cells; reduced serum lg	Mutations in the PAfPgene, leading to accumulation of toxic metabolites in lymphocytes
Defects in V(D)J Recombine	ation	
RAGI or RAG2 deficiency recombination*	Decreased T cells and B cells; reduced serum Ig; absence or deficiency of T and B cells	Cleavage defect during V(0)J recombination; mutations in RAG J or RAG2
Double-stranded break repair and checkpoint	Decreased T and B cells; reduced serum Ig, absence or deficiency of T cells and B cells	Failure to resolve hairpins during V(D)J recombination, mutations in ARTEMIS, DNA-PKcs, CERNUNNQS, LIG4, NBS1, MRE11, ATM
Defective Thymic Develops	nent	
Defective pre-TCR checkpoint	Decreased T cells; normal or reduced B cells; reduced serum Ig	Mutations in CD45, CD3D, CD3E, ORALJ (CRAC channel component) STIM1
DiGeorge syndrome	Decreased T cells; normal B cells; normal or reduced serum lg	22q11 deletion; T-box 1 (TBX1) transcription factor mutations
FoxNI deficiency	Thymic aplasia with defective T cell development	Recessive mutation in FOXN1
CFt a chair deficiency	No op T cells; y6 T cells normal; recurrent infections and autoimmunity	Autosomal recessive deletion in C region of TCR a chain
Defective T cell thymic gress and defective T cell ignaling	Marked reduction in all peripheral T cells	Mutations in RHOHand MSTJ
elective loss of CD4+ T ells and defective T cell gnaling	Decreased CD4+T cells	Mutations in LCKand UNCI 19
ther Defects		
eticular dysgenesis	Decreased T cells, B cells, and myeloid cells	Mutation in AK2
2014		on an aclaimm releas

Defec

Bare syndr

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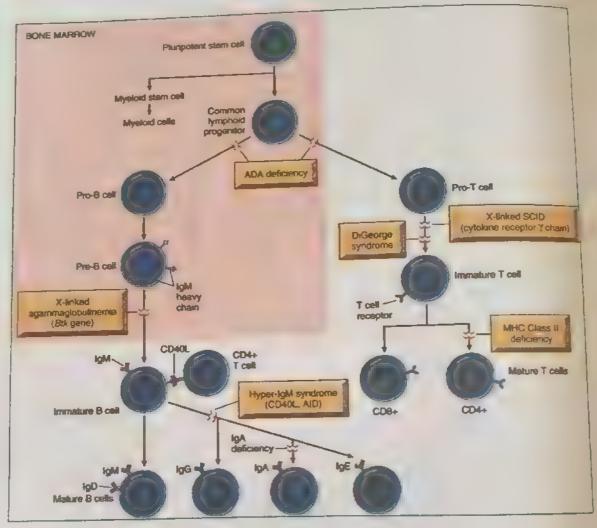
ADA, adenosine deaminase; AK2, adenylate kinase 2; ATM, ataxia-telangiectasia mutated; CRAC, calcium release activated channel, DNA-PKcs, DN A-dependent protein kinase catalytic subunit; UG4, DNA ligase 4, MRE11, metolic recombination homologue 11; NBS1, Nijmegert breakpoint syndrome 1; PNP, purine nucleoside phosphory-"Hypomorphic mutations in /MGgenes and in ARTEMIS can contribute to Omenn's syndrome.



ς,

	Defects in T Cell Activation	
Disease	Functional Deficiencies	Mechanism of Defect
Defects in MHC Expression	n	
Bare lymphocyte syndrome	Defective MHC class II expression and deficiency in CD4+ T cells; defective cell-mediated immunity and T-dependent humoral immune responses	Defects in transcription factors regulating MHC class II gene expression, including CliTA, RFXANK, RFX5, and RFXAP
MHC class I deficiency	Decreased MHC class I levels; reduced CDS+T cells	Mutations in TAP1, TAP2, and TAPASIN
Defective T Cell Signaling		
Proximal TCR signaling detects	Defects in cell-mediated immunity and T-cell—dependent humoral immunity	Mutations in CD3 genes, CD45, ST1M1,0RAI1
Wiskott-Aldrich syndrome Autosomal recessive WAS-1 ike disease	Defective T cell activation and leukocyte mobility Defective T cell activation and leukocyte mobility	TCR-dependent actin- cytoskeletal rearrangements are defective because of mutations in WAS, an- Xlinked gene mutation in WIP
Familial Hemophagocytic	Lymphohistrocytoses	
X-linked lymphoproliferative syndrome	Uncontrolled EBV-induced B cell proliferation, uncontrolled macrophage and CTL activation, defective NK cell and CTL function	Mutations in SAP Mutations in X-IAP
Perforin deficiencies	Uncontrolled macrophage and CTL activation, defective NK cell and CTL function	Mutations in PERFORIN
Granule fusion	Uncontrolled macrophage and CTL activation, defective NK cell and CTL function	Defective cytotoxic granule exocytosis; mutations in RAB27A, MUNC13-4, SYNTAX-IN, >5A?jand in iTSfin Chediak-Higashi syndrome-see Table 21-2)

AP3, adaptor-related protein complex 3; LYST, lysosomal trafficking regulator protein; SAP, SLAM-associated protein; TAP, transporter associated with antigen processing, WASP, Wiskott-Aldrich syndrome protein.



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Fig. 5.15:

#### 1. Deficiencies of B cell functions

- a. Infantile X linked agammaglobulinemia ~ Burton type agammglobulinemia Lack of mature B cells due to mutation in B cell tyrosine Kinase gene (B TK gene)
- Absence of igs, plasma cells & B cells
- Presents after 8- 9 months of birth (after maternal IgG has been catabolized)
- Septicemia + recurrent pyogenic infection (Staph, H. influenza)
- · Diarrhea Giardia
- Fungal + Viral infection handled normally
- b. Transient Hypogammaglobulinemia -
- Familial
- Males + Females
- Affects IgG alone
- More severe in premature infants (as IgG crosses late in pregnancy) disappears in first 3 yrs



- c. Common variable immunodeficiency:
- All have hypogammaglobulinema
- Affecting all classes sometimes IgG alone
- Recurrent sinopulmonary pyogenic infections
- Recurrent herpes virus infection
- Recurrent bacterial infections + giardiasis
- Autoimmunity RA, P.A, Hemolytic Anemia, lymph reticular malignancies (esp. in females) and gastric carcinoma
- Normal or near normal number of B cells in blood and lymphoid tissue but no plasma cells and antibodies
- d. Complement deficiency: C2 deficiency is the commonest
- Recurrent bacterial infections are common complications of most complement deficiency with C3 deficiency- opsonisation - severe pyogenic infection (Pneumonia, meningitis, septicemia)
- Deficiency of C5, 6, 7, 8, 9, recurrent Neisseria bacteremia
- Properdin deficiency meningococcal septicemia
- 2. Combined T cell + B cell: Severe combined immunodeficiency Disease (SCID) - develops within just 2 yrs - infants show delayed growth with recurrent bacterial, viral and fungal infections.

- a. Most common type is X-linked characterized by mutation in gamma chain subunit of several cytokine receptors (I12, I14, IL7, IL9, IL11, IL15) resulting in failure of lymphoid progenitors to be stimulated by many Cytokines especially IL-7
- b. Swiss type SCID Failure of lymphoid stem cell development, no lymphocytes, and AR disorder
- c. Adenosine deaminase deficiency (ADA). AR disorder, characterized by deficiency of enzyme adenosine deaminase
  - Accumulation of dioxyadenosine and deoxyadenosine tri PO4 both are toxic to lymphocytes
- d. The Bare lymphocyte syndrome HLA ags Class I or II not expressed.
- e. Ataxia Teleangiectasia, Defective T and B cell function | cell mediated immunity + | lg/. + lgE, Lymphoma

## 3. Deficiencies of T cell function:

- A. Di George's Syndrome due to failure of development of 3rd + 4th branchial arches (thyroid, parathyroid, parafollicullar cells of thyroid + ultimobranchial body)
- Infants total absence of CMI, hypocalcemic telangiectasia + congenital defects of heart + great vessels
- Circulating B cells can deal with pyogenic infection but suffer from opportunistic infection (pneumocystis carinii) fungal + viral infection
- b. Nezelof 's Syndrome X linked disorder
- thymic hypoplasia
- B cells + Ig levels are normal

DAMS

Type II

Type III

Type IV

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Reactive amyloido Hemodia

Familial Familial

types).

System

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DISORDERS OF IMMUNE SYSTEM | 153

## Active Recall

Type [

Type II

Type III

Type [V

Immunocyte dyscrasias with amyloidosis (primary amyloidosis)

Reactive systemic amyloidosis (secondary amyloidosis).

Hemodialysis-associated amyloidosts.

Familial Mediterranean fever.

Familial amyloidotic neuropathies (several types).

Systemic Senile Amyloidosis.

Senile cerebral

Endocrine

Medullary carcinoma of thyroid.

Islets of Langerhans.

Isolated atrial amyloidosis.

Bruton's

Agammaglobulinemia

Hyper IgM syndrome

Isolated IgA deficiency

DiGeorge Syndrome

SCID

Wiskott Aldrich

Syndrome

Ataxia telangectasia

Leucocyte adhesion molecule deficiency

Chediack Hegashi

Syndrome

Chronic granulomatous

disease

6

GENETICS

# CONCEPTS

Concept 6.1: Genetic Disorders



# Concept 6.1: Genetic Disorders

Learning Objectives: Mutations, chromosomal abnormalitites, Mendalian and non Mendalian inheritances, Single gene disorders, Gene therapy.

## **Time Needed**

1° reading	2 hours
2 <sup>nd</sup> reading	45 mins
Z Icading	The second secon

#### Genetic Disorders:

Genetics - Study of single / few genes & their phenotypic effects.

Genomics - Study of all genes in the genome and their interactions.

Proteomics - Measurement of all proteins expressed in a cell / tissue.

Bioinformatics - Biologists, Computer scientists, Mathematicians.

Pharmacogenomics - Individualized drug therapy.

#### Two strategies of characterize involved genes:

1. Functional cloning / Classics approach:

Done in inborn errors of metabolism e.g. phenylketonuria, disorders of Hb synthesis. Clinical phenotypes → Biochemical abnormality → abnormal protein → abnormal gene identified & studied.

2. Positional cloning / Candidate gene approach:

Initially ignores biochemical clues relies on mapping disease phenotypes to particular chromosomal location by cytogenetic studies or Linkage analysis e.g. Cystic fi- brosis, Neurofibromatosis, Duchenne mus- cle dystrophy, PCKD, Huntington disease.

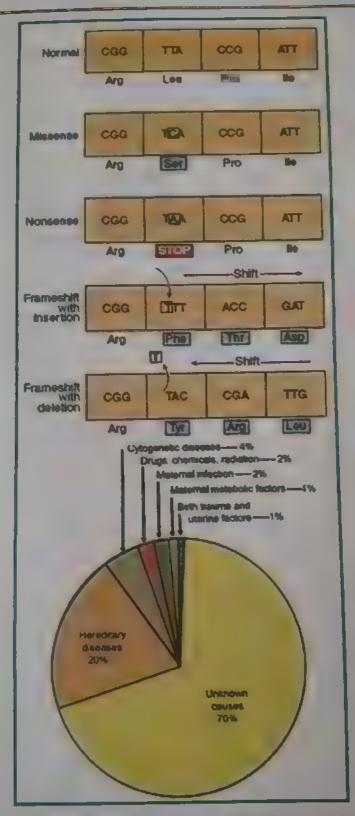
Mutant mice: Transgenic - molecularly cloned DNA introduced into mice →manifest human disease e.g. c-myc → tumors.

Gene knock out: replace (n) genes by inactive genes. E.g. Loss of both LDL receptor gene → hypercholesterolemia Benefits of genetic engineering.

- 1. Production of biologically active agents e.g. TPA, GH, Insulin, CSF.
- 2. Gene therapy.
- 3. Disease diagnoses: by molecular probes Mutation: Permanent change in DNA. Genome mutation: loss or gain of whole chromosome.

Chromosome mutation: rearrangement of genetic material, give rise to visible structural

Gene mutations: Affecting gene as single base pair e.g. point mutation. Insertion/ deletion, microdeletions, trinucleotide repeat mutation.



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Fig. 6.1: Causes of birth defects in humans. Most birth defect have unknown causes

Fig. 6.2: Sensitivity of specific organs to teratogenic agents at critical stages of human embryogenesis Exposure to adverse influences in preimplantation and early post implantation stages of development (far left) leads to prenatal death. Periods of maximum sensitivity to teratogens (horizontal bars) vary for different organ systems but overall are limited to the first weeks of pregnancy.

#### **Genetic Disorders:**

- 1. Disorders related to mutant genes of large effect (Mendelian disorder).
- 2. Disorders with multi-factorial inheritance.
- 3. Chromosome disorders.
- 4. Single gene disorders with non classic pattern of inheritance.

## Mendelian Disorders:

Dominant.

Recessive.

Co- dominance e.g. histocompatibility and BG Ag.

Single genes: 3 patterns of transmission: AD, AR, X Linked.

Reduced penetrance Individuals inherit the mutant gene but are phenotypically normal.

Variable expressivity: Trait seen in all individuals but expressed differently.

Pleiotropic Single mutant gene → many end effects.

Genetic heterogeneity: Mutations at several loci producing the same trait.

Autoson

pisease panilial h con Wille Hereditar Hereditar Octeoger Ehlers-E

> Marian Neurofi Huntin Retino Wilms

Famil Acute Heree

## tosomal Dominant Inheritance:

itosomal Dominant Inheritance: Representative Auto	somal Dominant Disorder	31
	Frequency	Chromosome
case . Lorentemia	1/500	19p
amilial hypercholesterolemia	1/8000	12p
Willebrand disease	1,5000	14, 8
ered,tary spherocytosis (major forms)	1/2500	1, 1p, 2q, 14
ereditary elliptocytosis (all forms)	1/10,000	17q, 7q
steogenesis imperfecta (types l-IV)	1/5000	2q
n.ers-Danlos syndrome type III	1/10,000	15q
afan syndrome	1/3500	17q
earofibromatosis type 1	1/15,000	4p
unt.ngton chorea	1/14,000	13q
et nohlastoma	1/10,000	llp
.ims tamor		5q
milial adenomatous polyposis	1/ 10,000	119
cate intermittent porphyria	1/15,000	
ereditary amyloidosis	1/100,000	18q
dalt polycystic kidney disease	1/1000	16p

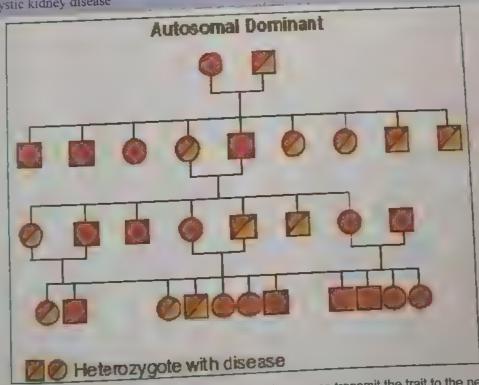


Fig. 6.3: Autosomal dominant inheritance. Only symptomatic persons transmit the trait to the next generation, and half the children have a chance of being symptomatic. Bath males and females are affected.

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- 1. An affected person usually has at least one affected parent
- 2. Affects either sex;
- 3. Transmitted by either sex;
- 4. A child of an affected x unaffected mating has a 50% chance of being affected (assuming the affected person is heterozygous)

#### **Autosomal Recessive:**

Republik	Marie Marie	
Disease	Frequency	Chrouosome
Cystic fibrosis	1/2500	other afternoon for
α-Thalassemia	High	16p
B-Thalassemia	High	11p
Sickle cell anemia	High	lip
Myeloperoxidase deficiency	1/2000	17q
Phenylketonuria	1/10,000	12q
Gaucher disease	1/1000	1q
Tay-Sachs disease	1 4000	15q
Hurler syndrome	1/100,000	22p
Glycogen storage disease la (von Gierke lisease)	1,100,000	17
Wilson disease	1/50,000	13q
Hereditary hemochromatosis	1 1000	6p
1-Antitrypsin deficiency	1/7000	434 444 - 14q
Oculocutaneous albinism	1 20,000	Ilq
Alkaptonuria	<1/100,000	3q
Metachromatic leukodystrophy	1/100,000	22q

Phenylketonuria, Galactosemia, Homocys-tinuria,

Lysosomal storage disease, at - AT deficiency, Wilson disease, Hemochromatosis Glycogen storage disease

Cystic fibrosis, Sickle cell anemia. Thalas- semias,

Congenital adrenal hyperplasia, E - D syn- drome (some variety), Alkaptonuria Neurogenic muscular atrophies

- 1. Affected people are usually born to unaffected parents;
- Parents of affected people are usually asymptomatic carriers;
- 3. There is an increased incidence of parental consanguinity;
- 4. Affects either sex:
- 5. After the birth of an affected child, each subsequent child has a 25% chance of being affected (assuming both parents are phenotypically normal carriers).



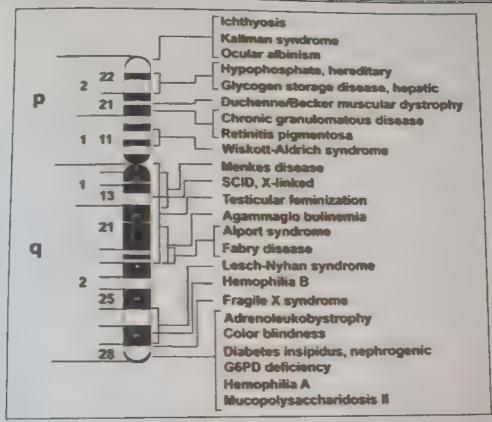


Fig. 6.4: Localization of representative inherited diseases on the X chromosome GGPD

#### X Linked Recessive:

Ducnenne muscular dystrophy, Hemophilia A & B Chronic granulomatous disease, G6PD deficiency Agammaglobulinmia, Wiskott Aldrich syndrome Diabetes insipid us, Leach-Nyhan syndrome,

- 1. Affects mainly males;
- 2. Affected males are usually born to unaffected parents: the mother is normally an asymptomatic carrier and may have affected male relatives;
- 3. Female may be affected if the father is affected and the mother is a carrier, or occasionally as a result of nonrandom X- inactivation.
- 4. There is no male-to-male transmission in the pedigree.

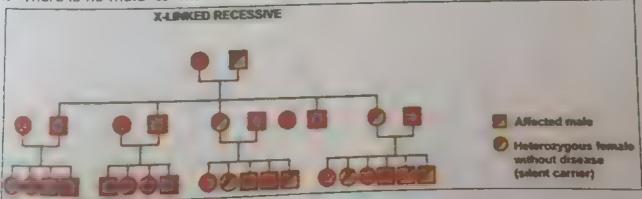


Fig. 6.5

#### X - Linked Dominant:

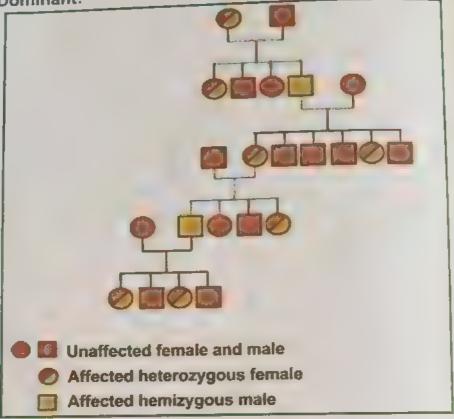


Fig. 6.6: X-linked dominant inheritance.

- 1. Affects either sex, but more females than males;
- 2. Females are often more mildly and more variably affected than males;
- 3. The child of an affected female, regardless of its sex, has a 50% chance of being affected
  - 4 For an affected male, all his daughters but none of his sons are affected

#### Y Linked Inheritance:

No Y-linked diseases are known as yet:

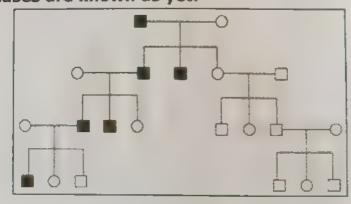


Fig. 6.7

Save for determinants that dictate male differentiation, the only characteristic that may be located on the Y chromosome is the attribute of hairy ears, which is not altogether devastating.

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- Affected males always have an affected father (unless there is a new mutation).
- 3. All sons of an affected man are affected.

# Mitochondrial Inheritance:

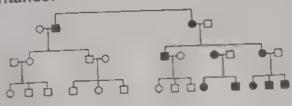


Fig. 6.8

Leber Hereditary optic neuropathy, MERRF (Myoclonic epilepsy with ragged red fibers) Leigh disease, mitochondrial encephalomyopathy, lactic acidosis and stroke llike episodes (MELAS).

- 1. Both males and females affected.
- 2. Affected females transmits to all males and females.
- 3. Affected male do not transmit the disease.

# Disorders associated with defects in structural proteins:

- Marfan syndrome: Connective tissue disorders, affecting skeleton, eyes &CVS, AD.
- Mutation of FBN 1 (chromosome, 5q21)
- Mutation of FBN 2 (chromosome 5q3) → congenital contractual arachnodactyly (AD).
- Mutation fibrillin disrupts assembly of
- (n) alleles also →Dominant negative.
- Skeletal abnormality → most striking features: Tall, long extremities, long tapering fingers and toes, US/LS ratio
- Lax 'joint ligaments, double jointed, long headed (dolichocephalic), prominent supraorbital ridges, bossing of frontal eminences deformed chest (as seen in Abraham
- Ocular: B/L outward and upward subluxation and dislocation of lens (Ectopia lentis).
- CVS : Most life threatening features: Mitral valve prolapse, Cystic medial necrosis ⇒ dilatation of aortic valvering and root →Aortic incompetence.
- MV lesions are more frequent but clinically less important than aortic lesion, Death from Rupture of aortic dissection / Cardiac failure.

## Ehlers - Danios syndrome:

- Result from defect in collagen synthesis or structure.
- 14 collagen types; 9 EDS variants, all 3 patterns of inheritance known.

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- Gen skin hyper extensible fragile hypermobile joints, joint dislocation.
- Various c/o Rupture of colon and large arteries: EDS type IV.
- Ocular fragility: EDS type VI.
  - Diaphragmatic hernia: EDS type I.
- Type VI: most common. AR from EDS.
  - Mutation in enzyme encoding lysyl hydroxylase (cross linking).
- Mutation in enzyme encoding 1/57.
   Type IV: AD, mutation affects gene for collagen Type III (abundant in blood vesser, 5
- Type VII: (a, b, c): abnormality in conver- sion of type I procollagen to collager,
- Type IX: Defect of Cu metabolism (mutation in copper binding protein ↓ act on ç. Copper lysyl oxidase.

## Disorders Associated with Defects in Receptor Proteins: Familial Hypercholesterolemia:

Most frequent Mendelian disorder. Abnormal LDL receptor →↑LDL in plasma → alternate scavenger pathway atheroscelerosis, xanthomas.

LDL receptor gene: Chromosome 19. Class I - rare, absent synthesis.

Class II - defect in transport of R. Class III - ↓ Binding of LDL with R.

Class IV - Failure to form coated Pits (clustering).

Class V - Recycling.

## Disorders Associated with Defects in Enzyme:

A. Lysosomal storage Disease. Lysosomal enzyme.

Synthesized in ER, transported to Golgi apparatus and undergo translation post translational modifications, Attachment of mannose - 6 phosphate groupings (address label), which is recognized by specific receptor on inner surface of Golgi membrane Helps in.

Segregation from other secretory proteins. Abnormal address label → LSD

Segre	Segregation from other secretory proteins. Abnormal address label → LSD.			
			Mucopolysneckaridesel	
Гуре	Eponym	Location of Gene	Chnical Features	
1 H	Hurler	4p16.3	Organomegaly, cardiac lesions, dysostosis multiplex corneil clouding, death in childhood	
IS	Scheie	4p16.3	Stiff joints, corneal clouding, normal intelligence, longevity	
Il	Hunter	X	Organomegaly, dysostosis multiplex, mental retardation, death earlier than 15 years of age	
III	Sanfilippo	12q 14	Mental retardation	
IV	Morquio	16q24	Skeletal deformities, corneal clouding	
V	Obsolete	-		
VJ	Maroteaux Lamy	5q13-14	Dysostosis multiplex, corneal clouding, death in second decade	
VII	Sly	7q21.t-22	Hepatosplenomegaly, dysostosis multiplex	

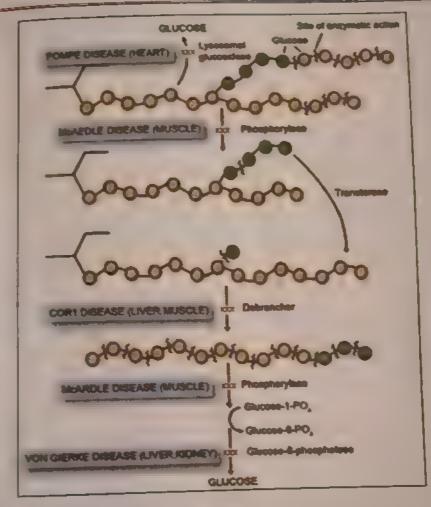


Fig. 6.9: Sequential catabolism of glycogen

#### TAY - Sachs Disease:

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- Most common form of GM2 gangliosidosis.
- Hexosaminidase a- unit deficiency.
- High prevalence in Jews: carrier rate is 1 in 30.
- GM2 ganglioside accumulates in heart, liver spleen etc.
- Main clinical presentation: CNS & ANS & Retina involved.
- Ganglion cells in retina: swollen particularly in margins of Macula \_ Cherry Red spot.
- L/M: Neurons ballooned with cytoplasmic vacuoles followed by destruction (Oil Red O, Sudan Black B positive).
- E/M: Cytoplasmic inclusions: whorled configuration within lysosomes composed of onion skin layers of membrane.
- C/F: Infants (n) at birth.
- S/S at 6 months of age (depend on
- severity of deficiency).
- Motor incoordination. Mental obtundation, muscle flaccidity, Blindness, dementia.
   Death 2-3 years of age.



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## Niemann Pick Disease:

- Deficiency of sphingomyelinase 

   accumulation of sphingomyelin
- Deficiency or springornyelliase
   (Previous grouped with N/P disease Type C primary defect in intracellular cholester) esterification and transport).
- Type A: severe, infantile from with extensive neurologic involvement.
- Progressive wasting and early death
- within first 3 years of life.
- Type B: No CNS involvement, survives into adulthood.
- L/M: affected cells are enlarged (upto
- 90 um in diameter) with innumerable small vacuoles foamy appearance of cytoplasm SBB/ Oil Red O positive.
- E/M: Vacuoles are enlarged secondary lysosomes.
- Contain membranous cytoplasmic bodies resembling lamellated myelin figures paralle. palisades - Zebra bodies.
- Gross: Splenomegaly, hepatomegaly, lymphadenopathy.
- Brain: Gyri are shrunken, sulci widened.
- Retinal cherry spot positive in 1/3 ½ pts.

#### Gaucher Disease:

Lysosomal storage disorder.

Deficiency of glucocerebrosidase, accumulation of glucocerebrosied in phagocytic cells.

### 3 Clinical subtypes:

Lynf	The O	THETT
Chronic non – neuropathic Limited to phagocytic cells	Acute neuronopathic (infantile acute cerebral pattern)	Intermediate pattern
Splenic & skeletal inv. Dominate  Jews +  Longevity – slightly"  1 (not absent) enzyme	CNS inv + HSM  CNS manifestation dominant No predilection for Jews Death at early age  No detectable enzyme in tissue	_

L/M: Gaucher cells seen in Virchow - Robin spaces.

## Diagnosis:

- For homozygote: measurement of glucocerebrosidase activity in peripheral blood leukocytes of cultured skin fibroblasts.
- Heterogotes: Detection of specific
- mutation.
- To differentiate from Pseudo Gaucher cells- iron (AIIMS question).



## Alkaptonuria (Ochronosis):

- First inborn error of metabolism to be discovered, AR.
- . Lack of Homogentisic oxidase, block metabolism of phenylalanine tyrosine > HA accumulation.
- . Gene for enzyme: chromosome 3q 21.
- . Homogentisic acid binds to collagen in connective tissue, tendons and cartilage
- → Blue black pigment → ochronosis.
- Cartilage become brittle and fibrillated.
- prime site of attack: vertebral column (intervertebral disc) later knees, shoulder hips.
- Small joints of hands and feet ->spared.

## Disorders associated with defects in proteins that regulate cell growth:

## 1. Neurofibromatosis type I (Von Recklinghausen disease):

- 1 in 3000.
- AD, chromosome 17q 11.2
- (nerofibromin).
- Expressivity variable, pentrance : 100%.
- 3 major features.
- Multiple neurofibromas dispersed
- anywhere on the body.
- Pigmented skin lésions café lait spots.
- Pigmented iris hamatomas Lisch nodules.
- Neurofibromas 3 types.
- Cutaneous.
- Subcutaneous.
- Plexiform → diffusely involves subcutaneous tissues contain numerous torturous thickened nerves (become malignant in 5 % of pts with NF -1.
- Cutaneous pigmentation: seen in 90% patients.
- Café au lait spots-round to ovoid, smooth border, over trunk parallel to underlying nerve (>6 in number, >
- 1.5 cm diameter).
- Pigmented hamartomas / Lisch nodules: seen in 94% patients older than 6 years.
- Other lesion:
- Skeletal lesion erosive defect, scoliosis intraosseous cystic lesion sub periosteal bone cyst, pseudoarthrosis of tibia.
- 1 risk of developing Wilm's tumor Rhabdomyosarcoma: Meningioma: Optic glioma; Pheochromocytoma
- 1 risk of developing CML.
- ↓IO.

## 2. Neurofibromatosis - Type: 2

- AD 1 in 40,000 to 50,000.
- B/L acoustic Schwannomas and multiple meningiomas



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- Gliomas (esp. ependymoma) of spinal cord Schwannosis, Meningio angiomatosis
- glial harmartomas Lisch nodules are not found
- Chromosome 22q 12 (product merlin)

# Disorders with multifactorial inheritance:

Combined action of environmental influences and two or more mutant genes having Combined action of environmental infloating characters: hair color, eye color, height, intelligence.

Cieft lip or cieft palate - Congenital heart

disease Coronary heart disease - Hypertension Gout - Diabetes mellitus

Pyloric stenosis - Club foot

## Normal karyotype:

Karyotype is standard arrangement of photographed or imaged stained metaphase spread in which chromosome pairs are arranged in order of decreasing length.

Staining G banding (400 - 800 bands per haploid set).

Autosomes: grouping -> (according to length, decreasing order & shape).

Group A: Chromosome 1to 3 Group B: Chromosome 4, 5

Group C: Chromosome 6 to 12 Group D: Chromosome 13-15 Group E: Chromosome 16-18 Group F: Chromosome 19-20 Group G: Chromosome 21, 22

Metacentric chromosomes: Centromere in middle: GP - A&F.

## Cytogenetic disorders:

Sub metacentric centromere toward one end: GP - B, C E.

Acrocentric chromosomes: Centromere near tip: GP -D, G.

Sex chromosomes: X with C group

Y with G group (or placed in Right hand corner).

FTSH - study chromosomes in inter -phase nuclei also.

Subtle microdeletions and complex translocations detected with DNA probes, localize gene to a specific site.

Chromosome painting: Type of FISH: Whole chromosome labeled with fluorescent DNA probes at multiple sites. Spectral Karyotyping (SKY): ALL 46 chromosomes visualized simultaneously using 5 fluorochromes & computer aided signals.

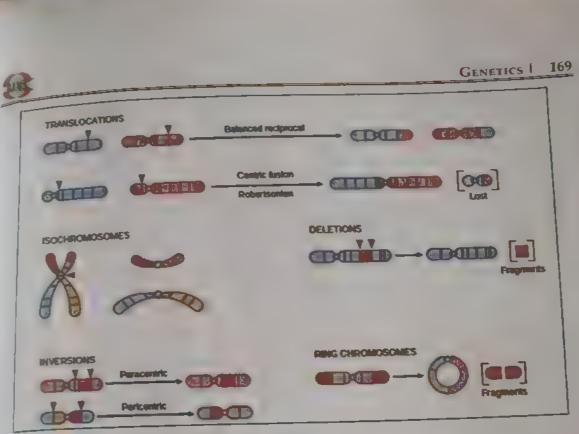


Fig. 6.10

Any exact multiple of haploid is called 'Euploid'.

Not an exact multiple of haploid: 'Aneuploid' (Causes: Non disjunction & Anaphase lag) Monosomy or Trisomy of sex chromosome

- Compatible with life - associated with

variable degrees of phenotypic abnormality Monosomy of Autosome - gen. do not permit

Trisomy of Autosome → (with exception or Down syndrome) severally handicapped, die survival.

Mosaicism > 2 or more cell populations in same individual, d/t mitotic errors in early development.

Autosomal mosarcism is much less commo Changes / Abnormality in structure.

## Studied using FISH / SKY:

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- 1. Deletion: loss of a portion of chromosome
  - a. Terminal / Interstitial e.g. .46 x 4, Del (16) P (14).
  - b. Ring chromosome: special form of deletion occurring at both ends with fusion of damaged ends.
- 2. Inversion: Two breaks within a single chromosome with inverted reincorporation of segment.
  - Paracentric inv only one arm. Pericentric breaks on opposite sides of centromere.
- 3. Isochoromosome: One arm is lost, remaining arm is duplicated.
- 4. Translocation: segment from one chromosome is translocated to other balanced reciprocal translocation.
- 5. Robertsonian translocation / or centric fusion: B/W two acrocentric chromosome Forming abnormally long chromosome and abnormally short chromosome (lost) 1 risk of producing abnormal gametes

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\* 7.5 % of all conceptions have a chromosomal abnormality, most of which are not compatible with survival or live birth.

 Chromosomal abnormalities are identified in 50 % of early spontaneous abortuses
 Chromosomal abnormalities are identified in jmmediate postnatal period and in 5% of still births and infants who die in immediate postnatal period.

In live born infant, free is 0.5 -1%.

#### Trisomy 21 (Down syndrome):

Most common chromosomal disorder Major cause of mental retardation Incidence: 1 in 700 Maternal age: Incidence of 1 in 25 live births for mother > 45 years

#### Karyotypes:

→ 95% - Trisomy 21 (Meiotic non - disjunction in ovum).

4% - Translocation and 1% - Mosaic non disjunction).

#### Morphology:

- Epicanthic fold flat facial profile.
- Mental retardation: 80% IQ = 25-50.
- Abundant neck skin.
- Simian crease.
- Congenital heart defect (in 40% of patients): Most common are defects of endocardial cushion. Including ostium primum, ASD, A
- V valve malformation VSD.
- intestinal stenosis.
- umbilical hernia.
- predisposition to leukemia (All and AML
- -M7) (10-20 times ↑) Most common leukemia is ALL and most specific leukemia is AML M7.
- Hypotonia.
- Gap between 1st and 2nd toe.
- After 40 years → Alzheimer's disease.
- 80% survival tili 30 years.

#### Trisomy 18 (Edward syndrome): 1 in 8000:

90% - trisomy 18 - Maternal age T 10% mosaic - Maternal age (n).

#### Morphology:

- Prominent occiput.
- Mental retardation.
- Micrognathia.
- Low set ears, overlapping fingers.
- Short neck.
- Cardiac, renal, intestinal defects.
- Rocker bottom feet.
- Limited hip abduction.
- Rarely survive after 1 years of age.

## Patau syndrome (Trisomy 13) 1 in 15.000:

Trisomy 13

Translocation type (maternal age not implicated) Mosaic type.

Morphology.

MICTOC

polyda

cleft ! Cardia

Umbil ROCKE

Rarel

Cri du ch 46XX, 5P

. mer

mer mic

Epi

Chromo Clinical delay, va previous Velocard

DI Geor parathy



- . Microcephaly, micropthalmia. mental retardation, Holoprosencephaly.
- · Polydactyly.
- · Cleft lip and palate.
- · Cardiac and Renal defect.
- Umbilical hernia.
- Rocker bottom feet.
- · Rarely survival after 1 year of life.

## Cri du chat (cat cry) syndrome : 1 in 50,000:

46XX, 5P - Maternal age in normal. 46XY, 5P

- mental retardation.
- mewing cry.
- microcephaly and round facies.
- Epicanthic folds.

## Chromosome 22q 11 deletion syndrome:

Clinical feature: Cong. HD, Abnormality of palate, facial dysmorphism, development delay, variable degree of T cell immunodef. & hypocalcaemia.

Previously thought to be 2 disorder - Di George syndrome.

Velocardiofacial syndrome

Di George syndrome: Thymic hypoplasia →T cell immunodef.

Parathyroid hypoplasia -> hypocalcemia

Sperm Ovum	х		Υ		XY		0			
x	46,XX Normal 2	0	46,XY Normal of	0	47,XXY Ithodobar d	<b>(6)</b>	45,X Turner 9	0		
хх	47,XXX		47,XXY	•	48,XXXXY Kindular d		46,XX Normal ♀	0		
XXX	48,XXXX 9	0	48,XXXXY	(6)	49,XXXXX		47 XXX Telplo X S			
0	45,X Turner 9	0	45,Y LETHAL		46,XY LETHAL		44 LETHAL			
	X chromatin (Sarr body) Y chromatin									

Fig. 6.11: Numerical aberrations of sex chromosomes Nondisjunction in either the male or female gametes is the principal cause of these abnormalities.

Velocardiofacial syndrome: Facial dysmorphism cleft palate, CVS abnormality, learning disability acronym 'catch 22

C - Cardiac abnormality A - Abnormal defect

T - T Cell defect C - Cleft plate

H – Hypocalcemia



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Diagnosis - FISH, Molecular basis - NK Cytogenetic disorders inv. sex chromosomes: More common than autosomal. Better tolerated.

## Lyon hypothesis:

- 1. only one X chromosome is genetically active.
- only one X chromosome is generically occurs at random in all cells of blastocysts
   inactivation of other X (maternal / paternal) occurs at random in all cells of blastocysts on day 16 of embryonic life.
- Inactive X chr seen as Barr body or X chromatin.
- Many genes may escape X inactivation (i.e. why 45X →Turner syndrome).
- 5. Also inactive X selectivity reactivity before first meiotic division.

## Sex chromosomal abnormality:

Subtle chronic problems related to fertility and sex development.

Difficult to diagnose at birth, recognized at

time of puberty.

Higher the number of X chromosome, the greater the likehood of mental retardation.

## Klinefelter syndrome: Male hypogonadism:

 $\geq$  2X  $\geq$  1Y chromosome (47 XXY, 46 XY/ 47 XXY).

1 in 850 live births.

Morphology: testicular atrophy & hyalinization, Eunuchoid body habitus: ↑ sole to os publis length gynecomastria Mean IQ: Lower than (n) (but not MR). Plasma FSH Testosterone ↓ Estradiol ↑

Cause: maternal non dysjunction / paternal non disjunction (ass with maternal age 1)

Variant: 48, xxxy, 49, xxxxy, 48 xxyy

## Turner syndrome:

1 in 3000 females birth, 99% of 45 X conceptuses - Non viable.

Complete or partial monosomy of x chromosome Hypogonadism in phenotypic females.

57% - 45 XO

14 % - structural abnormality 46, X, I (X) (q 10)

46, X, r(X)

46, X, del (Xq) 46, X del (XP)

29% - Mosaics 45x/ 46XX

45X/46 XY

45X/ 47XXX

45X/46 X, 1 (X) (q 10).

Morphology - short stature, commonest cause of primary amenorrhea, infertility, webbing of neck, cubitis valgus, peripheral lymphoedema at birth, board chest and wide spaced nipples, low posterior hairline pigmented nevi, coarctation of aorta preductal) and bicuspid aortic valves, streak ovaries.

CVS anomalies → single most important cause of mortality.

## Single gene disorders with non - classic inheritance:

Disease caused by triple repeat mutations Disease caused by mutations in mitochondrial genes.

Disease associated with genomic imprinting. Disease associated with gonadal mosaicism.

3									_		_			(	GENE	TICS
	Repeat Normal -No. of Repeats Disease		55-200 (pis); >230 (full)	34-80 (pre); >100 (full)	34-80 (pre); >100 (full)		38-62	36-121	49–33	39 32	37. 63	30-03	, 55-84	21 33		37-306
	Normal		9-55	7-34	5-37		9-36	6-35	6-35	6-44		15-31	12-40	4		1 4 35
	Repeat		CGG	GAA	CTG		CAG	CAG	CAG	CAG	2	CVQ	. CAG	r CAG		CAG
	Protein		FMR-1 Protein (FMRP)	Frataxin	Myotonic dystrophy protein kinase (DMPK)		Androgen receptor (AR)	Huntingtin	Atrophin-1		Ataxin-1	Ataxin-2	Ataxin-3	to the second	al A-voltage-dependent	Ataxin-7
	- snoogh		Xq27.3	9921.1	19q13.3		Xq12 ·	4p16.3	12p13.31		6p23	12q24.1	14q21		19p13.3	3914.1
	Сене	Regions	FMRI (FRAXA)	FXN	DMPX	Suoi	AR	HTTT	ATNL		ATXN1	ATXN2	ATXN3		CACNAZA	ATXN7
Triple repeat mutation:	SANCE NO.	Expansions Affecting Noncoding Regions	fragile X syndroms	Friedreich ataxia	Myotonic dystrophy	Expansions Affecting Coding Regions	Spinobulbar muscular atrophy (Kennedy disease)	Huntington disease	Dentatorubial-pallidoluysian atrophy (Haw River syndroms)		Spinocerebellar ataxia type 1	Chinocerehellar ataxia type 2	Spinocerebellar ataxia type 3	(Machado-Joseph disease)	Spinocerebellar ataxia type 6	Spinocerebellar ataxia type 7

#### PATHOLOGY

Mutation is characterized by long repeating sequence of 3 nucleotides.

Mutation is characterized by long reposition differs in various disorders, in Specific nucleotide sequence undergoing amplification differs in various disorders, in most cases, share nucleotides G and C. Exan

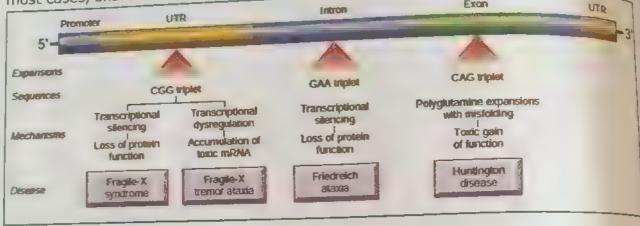


Fig. 6.12:

## Fragile X syndrome:

2<sup>nd</sup> most common cause of MR after Down syndrome.

X linked characterized by unusual mutation within FMR - 1 gene (Familial mental retardation-1).

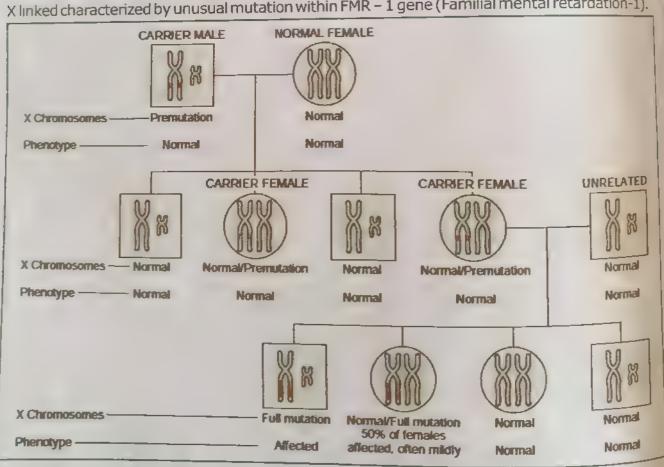


Fig. 6.13:

Note tha oogenes

next ger only 50° Alteration -> appe Males, orchidis

(N) P Permi Full T perm

> Othe Not Oog



Note that in the first generation all sons are normal and all females are carriers. During organisms in the carrier female, premutation expands to full mutation; hence, in the next generation all males who inherit the X with full mutation are affected. However, only 50% of females who inherit the full mutation are affected, and only mildly.

Alteration seen as discontinuity of staining or constrictions in long arm of X chromosome

appears broken --- fragile site.

Males, IQ:20 - 60; long faces, large mandible, large ears hyper extensibility Macro – orchidism (-> distinctive feature)

- X linked disorder.
- Presence of carrier males (transmitting male).
- Affected females: 50% of carrier females are affected.
- Risk of phenotype effects Risk depends of position of individual in pedigree
   "Sherman's paradox.
- Anticipation: clinical feat worsens with successive generation.
- Mutation: Xq 27.3, FMR -1 gene contains CGG multiple tandem repeats

(N) pop; CGG repeats; 6-46.

Permutation: 50-230 CGG repeats (N) transmitting males & carrier females.

Full mutation; 230-4000 CGG repeats. During oogenesis (but not in spermatogenesis) permutation → mutations by triplet amplification.

# Other diseases associated with nucleotide repeats: Not always triplets: Expansion:

Oogenesis → Fragile X syndrome. Spermatogenesis → Huntington's disease.

Affecting was Coding Regions	Affecting Coding Regions	
Fragile X syndrome	Spinobulbar muscular	
Myotonic dystrophy	atrophy (Kennedy disease)	
Freidrichs ataxia	Huntington's disease	
Progressive myoclonus epilepsy	Dentorubropallidolu- sian atrophy	

## Mutations in mitochondrial genes:

- Maternal inheritance (Ova contain MT within their abundant cytoplasm).
- (enzymes inv.in oxidative phosphorylation).

E.g. Leber Hereditary optic neuropathy-progressive B/L loss of central vision.

Neurodegenerative disease other mitochondrial encephelomyopathies: Leigh disease.

Myoclonic epilepsy and ragged red fibresmit DNA.

Mitochondrial encephalopathy, lactic acidosis and stroke like episodes.

### Genomic imprinting:

Imprinting; Selective inactivation of either maternal or paternal allele e. g
Maternal imprinting – Inactivation / Silencing of maternal allele.

 Prader willi syndrome: MR obesity, short stature, hypotonia, hypogonadism -Deletion on chromosome 15 band q 12 (affects paternally derived chromosomes).



2. Angelman syndrome; deletion of same region on maternally derived chromosomes,

MR, ataxia of inappropriate laughter- 'happy' puppets.

Also because of uniparental disomy.

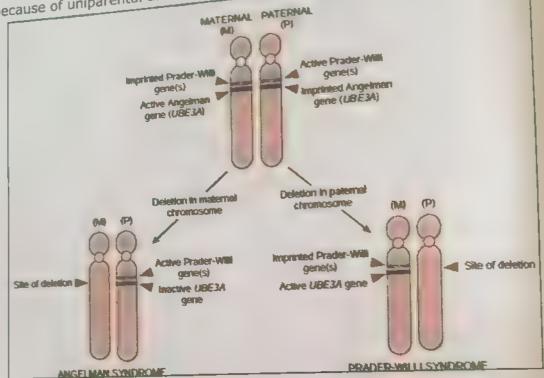


Fig. 6.14:

The molecular basis of these two syndromes lies in the genomic imprinting. Three mechanisms are involved.

- 1. **Deletions.** It is known that a gene or set of genes on maternal chromosome 15q12 is imprinted (and hence silenced), and thus the only functional allele(s) are provided by the paternal chromosome. When these are lost as a result of a deletion, the person develops Prader-Willi syndrome. Conversely, a distinct gene that also maps to the same region of chromosome 15 is imprinted on the paternal chromosome. Only the maternally derived allele of this gene is normally active. Deletion of this maternal gene on chromosome 15 gives rise to the Angelman syndrome. Deletions account for about 70% cases.
- 2. Uniparental disomy. Molecular studies of cytogenetically normal patients with the Prader-Willi syndrome (i.e., those without the deletion) have revealed that they have two maternal copies of chromosome 15. Inheritance of both chromosomes of a pair from one parent is called uniparental disomy. The net effect is the same (i.e., the person does not have a functional set of genes from the [nonimprinted] paternal chromosomes 15). Angelman syndrome, as might be expected, can also result from uniparental disomy of paternal chromosome 15. This is the second most common mechanism responsible for 20% to 25% cases.
- 3. Defective imprinting. In a small minority of patients (1% to 4%), there is an imprinting defect. In some patients with Prader-Willi syndrome, the paternal chromosome carries the maternal imprint and conversely in Angelman syndrome the maternal chromosome carries the paternal imprint (hence there are no functional alleles).

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the sc Molecu Genomi CONA P Oligon Rib pro In

> LO pro FIL Ta W

> > b

Pol Sev stat Mg( Hea

> Ani Ext Re



## Gonadal Mosaicism:

Results from mutation that occurs post zygotically during early (embryonic)

 If mutation affects only cells destined to form gonads, gametes carry mutation but the somatic cells are completely normal.

## Molecular Diagnostics:

Genomic probes - derived from a region of DNA.

CDNA probe-derived from RNA by reverse transcriptase.

Oligonucleotide probe - synthetic probe (Genomic & cDNA probes from cellular material). Rib probe - prepared by in vitro transcription system.

1. In situ Hybridization (ISH).

Localizes DNA or RNA directly in an intact cell by hybridization and radiolabelled probing FISH.

2. Filter hybridization.

Target DNA/RNA is extracted immobilized on nitrocellulose filter or nylon & hybridized with labeled probe

- a. Slot and dot blots: DNA is not fractionated before immobilizing.
- b. Southern blot DNA fractionation followed by gel electrophoresis.
- c. Northern blot Similar to southern blot but involves RNA.
- d. Western blot Proteinfractionation and antibodies are used as probes.

## Polymerase chain reaction (PCR):

Several millions of copies are formed from a single DNA fragment using a primer, heat stab e DNA polymerase (Taq polymerase) d- NTP (decoy nucleotide. d ATP, d CTP, d TTP) MgC12 and buffer in a thermo cycler. Each cycle consists of 3 steps.

Heat denaturation of DNA (at 94°C for 60-90 sec).

Annealing of primers (at 55°C for 30-120 sec).

Extension using DNA polymerase (at 72°C for 60-180 sec).

Repeated cycles done in automated thermal cycler.

#### Advantages:

Can be done on living or dead tissue. Small amounts of initial DNA template. sensitivity. Rapidity.

Amenability of automation.

No need for radionucliotide probes.

### Indirect DNA diagnosis linkage analysis:

- A. Site Polymorphisms (RELP) Natural DNA variations like single base pair changes may abolish or create recognition sites for restriction enzymes, thereby altering the length of DNA fragments product after digestion with certain restriction enzymes. Using appropriate DNA probes that hybridize with sequences in the vicinity of the polymorphic sites, DNA fragments.
- B. Length polymorphisms satellites are short repetitive sequences of noncoding DNA.



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Microsatellites – 2 to 6 pairs. Minisatellites – larger, usually 15-70 base pair.

## **Antenatal Diagnosis:**

Chorionic villus sampling (CVS). Amniocentesis. Cordocentesis (PUBS). Maternal serum AFP. Fetal cell in maternal blood.

### Gene therapy:

produci
dase

## Methods of Gene therapy:

Cell fusion.

Co precipitation / Transfection. Electroporation.

Liposome fusion.

Direct introduction of naked DNA. Viral vectors - Adenovirus, retrovirus.



#### Worksheet

. Chapter of DQB to be done:

. EXTRA POINTS FROM DQB



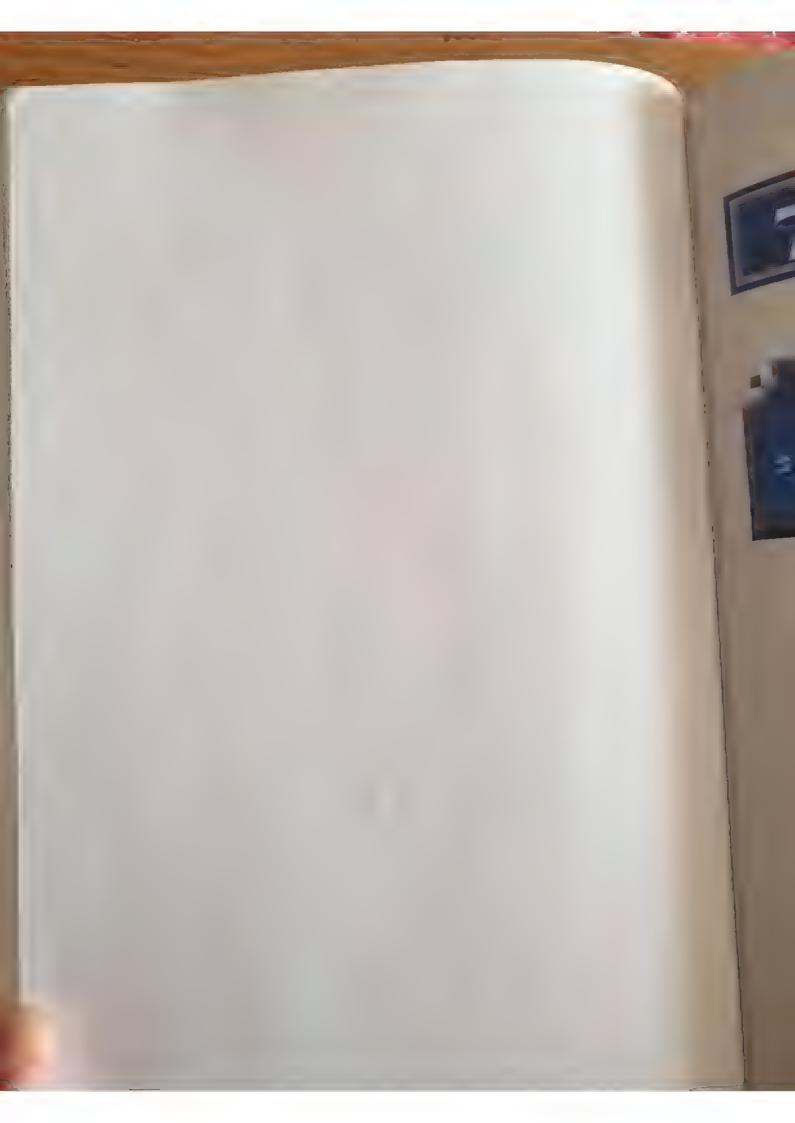
## Active Recall

Autosomal Dominan			TO STATE OF THE PARTY OF THE PA
	Chramosome	Disease	
Familial hypercholesterolemia		Cystic fibrosis	
, von Willebrand disease		α-Thalassemia	
Hereditary spherocytosis (major forms)		β-Thalassemia	
Hereditary elliptocytosis (all forms)		Sickle cell anemia	
Osteogenesis imperfecta (types 14V)		Myeloperoxidase deficiency	
Fhlers-Danlos syndrome type III		Phenylketonuria	
Marfan syndrome		Gaucher disease	
Neurofibromatosis type 1		Tay-Sachs disease	
Huntington chorea		Hurler syndrome	
Retinoblastoma		Glycogen storage disease la (von Gierke disease)	
Wilms tumor		Wilson disease	
Familial adenomatous polyposis		Hereditary hemochromatosis	
Acute intermittent porphyria		al-Antitrypsm deficiency	
Hereditary amyloidosis		Oculocutaneous albinism	
Adult polycystic kidney disease		Alkaptonuria	
		Metachromatic leukodystrophy	

[ Imprinting disorder ]	Physiological imprinting in tank	
Prader-willi syndrome		
Angelman Syndrome	200	

Primaclastide distance	Report	To Deinstein Duois on Lawren	
Fragile X syndrome			
Huntington Chorea			
Friedreich ataxıa			
Myotonic dystrophy			





BLOOD VESSELS

## CONCEPTS

= Concept 7 | Blood Vessels

## **Concept 7.1: Blood Vessels**

Learning Objectives: Atherosclerosis, vasculitis

### Time Needed

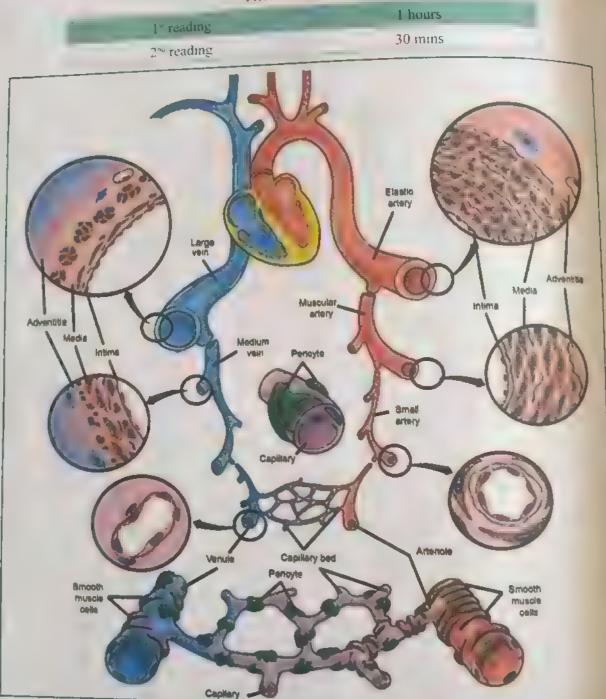


Fig. 7.1: Subdivisions and histologic structure of the vascular system. Each subdivision is subject to a set of pathologic changes conditioned by the structure-function relationship of that part of the system. For example the aorta, an elastic artery subject to great pressure, frequently shown a pathologic dilation (aneurysm) if the supporting elastic media is damaged. Muscular arteries are the most significant site of atherosclerosis. Small arteries particularly arterioles are sites hypertensive changes. Capillary beds, venules and veins each display their own types of pathologic changes.

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## Diseases of Blood Vessels:

Endothelial cells contain Weibel Palade bodies that are the storage organelle for VWF. Markers for endothelial cells are Factor 8 related antigen (Ab to VWF) and

Arteriosclerosis means hardenings of arteries.

Most prevalent and clinically significant arterial disease is Atherosclerosis, which is characterized by formation of intimal fibrous plaques with lipid core.

Arteriolosclerosis effects small arterioles and arterioles. Whole vessel wall is affected. May be hyaline or hyperplastic.

- , Hyaline Benign hypertension, DM, benign nephrosclerosis.
- · Hyperplastic Onion skin, concentric, laminated thickening microscopically in malignant hypertension, malignant nephrosclerosis.

Monckeberg's medial scierosis seen in patients above 50 years. Ring like dystrophic calcification within the media of medium to small sized muscular arteries. May undergo ossification. Intima + adventitia normal. No narrowing or inflammation seen. Femoral, tibial, radial + ulnar arteries are affected.

#### Atherosclerosis:

plaque) fatty Atheroma (fibro fundamental lesion. Affects elastic arteries and large and medium muscular arteries. Major consequences are ME, Stroke, aortic aneurysm and gangrene of extremities.

Sites in descending order of involvement are abdominal aorta, coronary artery, popliteal a, descending thoracic aorta, internal carotid artery, circle of Willis.

Vessels spared are upper extremity, mesenteric A, renal A.

Complications of plaque are thrombosis, rupture, hemorrhage, weakening of wall and development of aneurysm, calcification and atheroemboli.

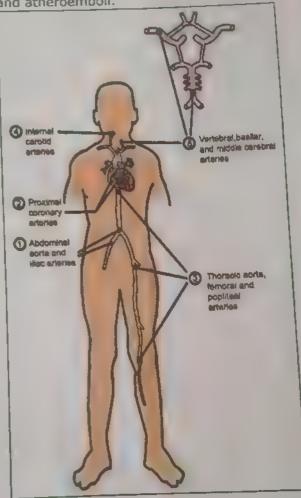


Fig. 7.2: Sites of servere atherosclerosis in order of frequency.

Fatty streaks may be precursors of AS plaques. Fatty dots are less than 1 mm in size. Both are sub- intimal foam cell collections. Not all fatty streaks become plaques.

American Heart association defines six types of lesions.

Iype 1- Fatty dot

Type 2- Fatty streak

Type 3-2 - Small extra cellular hpid pools

Type 4-2 - Core of extra cellular hpid pools

Type 5- Fibroa atheroma

Type 6- Complicated lesions (ulceration / haemorrhage / thrombosis

Clinically silent

Clinically silent

Clinically silent

Clinically silent

Clinically silent

Increased collagen and smooth muscle. Complication present

Increased collagen and smooth muscle. Complication present

Increased collagen and smooth muscle. Complication present

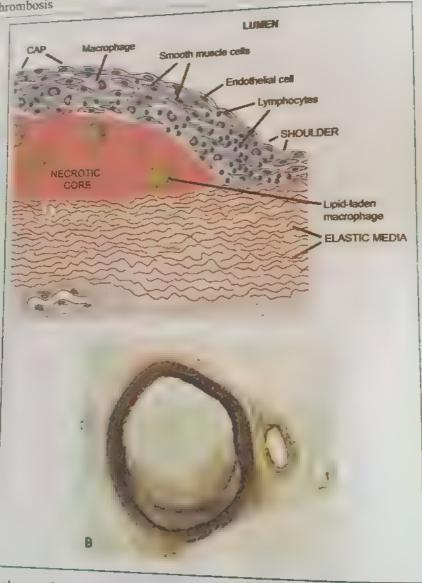


Fig 7.3: Fibrofatty plaque of atherosclerosis A in this fully developed fibrous plaque, the core contains lipid-muscle cells which produce collagen, small amounts of elastin, and glycosaminoglycans fibrous cap frequently appears intact. B. Adaptive stage with atherosclerotic plaque and vessel wall dilatation to maintain the normal size of the lumen. Normal artery wall is at the top.

Risk far Risk far Risk far Risk far Major ri Major ri HDL is G HDL is G HDL in G HDL off Common Type 1 Cut off

Triglyc

High II

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## Risk factors:

Disease of middle age Men> women. Familial disposition Major risk factor are- \* Smoking \* Hypertension \* Hyperhipidemia \* Diabetes Lipid -LDL and TG are bad.

HDL is good. Involved in reverse transport of cholesterol.

HOL increases with exercise and moderate consumption of ethanol.

HDL decreases with obesity and smoking. Dyslipoproteinemia Acquired - nephrotic syndrome, alcoholism, DM, hypothyroidism Genetic.

Commonest is Type 2(and b included), or Type 4.

Type 1 has no risk of atheroscierosis.

Cut off points for Cholesterol are < 200 mg%.

Triglycerides < 100 mg%. LDL < 150 mg%.

High intake of fish oils rich in omega 3 fatty acids leads to decreased LDL, and Platelet

agaregability	increased lipid	lnçiaei —	
1 pe l Chylomicrons	TG	Less than	Abn lipoprotein lipase, non atherogenic.
T . LDL	Cholesterol	. 10%	Mutation in the LDL receptor gene and Apo lipoprotein B gene.
1 pe 2b LDL and VLDL	Cholesterol and triglycerides	40%	Mutation in the LDL receptor gene and Apo lipoprotein B gene.
Remnant Chylomicrons and IDL	Triglycerides and Cholesterol	<1	Mutations in Apo lipoprotein E genes
Type 4 VLDL	Triglycerides	45%	Mutation of Lipoprotein lipase.
Type S VI DL and Chylomicron	Triglycerides and Cholesterol	5%	Apo hpoprotem C2 abnormalities.

Fig. 7.4: Complicated lesions of atherosclerosis. The luminal surface of the abdominal aorta and the common iliac artenes shows numerous fibrous plaques and raised, ulcerated lesions containing friable, atheromatous debris. The distal portion of the aorta displays a small aneurysmal dilation

#### HYPERTENSION:

Stronger risk above 45 years of age.

#### Minor-

- · Obesity.
- OCPs.
- Sedentary habits.
- Stress.
- · Family history.
- Age.
- · Male.
- High carbohydrate diet.
- Hyperhomocysteinaemia (causes endo- thelia dysfunction).
- Type A personality.

Markers of atherosclerosis are increased plasminogen activator, CRP, LP (a) which is an abnormal altered LDI abnormal altered LDL

2 risk factors increase risk 4 fold

3 risk factors increase risk 7 fold.

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# Types and Causes of Hypertension (Systolic and Diastolic):

Hypothyroidism (myxedema). Hyperthyroidism (thyrotoxicosis) Pregnancy-induced

Cardiovascular

Coarctation of aorta. Polyarteritis nodosa.

Increased intravascular volume. Increased cardiac output.

R gidity of the aorta

Neuro ogic

Psychogenic.

Increased intracranial pressure. Sleep apnea.

Acute stress, including surgery.

Pathogenesis:

1. Reaction to injury hypothesis. As is a chronic inflammatory response of arterial wall to endothelial injury.

Endothelial injury may be due to hyperlipidemia, HT, Smoking, Homocysteine, hemodynamic stresses, toxins, virus, immune.

Chronic endothelial injury

Endothelial dysfunction (Increased permeability and leukocyte adhesion)

Smooth muscle migration from media to intima

Macrophages and smooth muscle engulf lipid

Proliferation of smooth muscle / collagen and ECM proliferation

- 2. Monoclonal hypothesis Smooth muscle proliferation is the primary event.
- 3. Infective Chlamydia pneumonia, HSV, CMV are implicated.

Hypertensive vascular disease:

90-95% are idiopathic, 5 - 10% are renal Renal dysfunction is essential for development and maintenance of

hypertension.

Essential HT- Polygenic inheritance / environmental.

Single gene disorders associated with HT are:

- Abnormal aldosterone synthase.
- 11 β hydroxylase deficiency.
- 3.  $17 \alpha$  hydroxylase deficiency.
- 4. Liddle syndrome ( $\beta$  or  $\gamma$  subunit of epi Na channel).
- 5. Gillman syndrome (Na Cl contransporter def).
- 6. Pseudohypoaldosteronism (a or b subunit of Epi Na channel).

6. Pseudonypoaidosteronism (c. c. s. s. obesity, smoking, physical inactivity, increased Environmental factors include stress, obesity, smoking, physical inactivity, increased

salt intake.

Mechanisms are renal retention of sodium and vasoconstriction and vascular hypertrophy.

Large - Accelerated atherogenesis, weakens the wall and predisposes to aneurysm and dissection.

Small - Hyaline and hyperplastic arteriolosclerosis.

Hyaline - Homogeneous pink thickening of arteriolar wall with loss of structural deta and narrowing of lumen. Due to leakage of plasma proteins and ECM production by smooth muscles.

Hyperplastic - Seen in malignant hypertension (Diastolic BP> 100). Onion skin concentric laminated thickening, reduplicated basement membrane, fibrinoid necrosis (Necrotising arteriloitis). Changes esp seen in kidney.

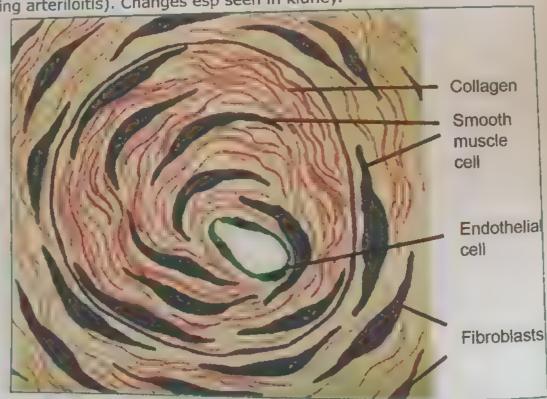


Fig. 7.5: Arteriolosclerosis. In cams of hypertension, the arterioles exhibit smooth muscle cell proliferation and increased amounts of intercellular collagen and glycosaminoglycans, resulting in an 'onionskin' appearance The mass of smooth muscle and associated elements tends to fix the size of the lumen and restrict the arteriole's capacity to dilate.

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## Vasculitis:

Denotes inflammation of vessel wall. Two mechanisms. Direct (Toxins, microbes, irradiation, mechanical trauma) a and

immunologic.

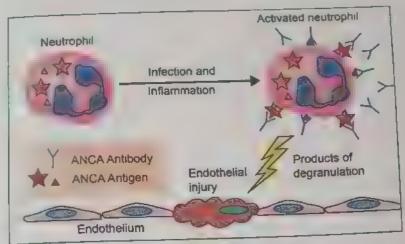


Fig. 7.6: Model of the pathogenesis of antineutrophil cytoplasmic antibodies (ANCA) vasculitis. ANCA antigens are normally found in the neutrophil cytoplasm with very little surface expression. In inflammation and infection increased cell surface expression of ANCA antigens is induced in the neutrophils. ANCA present in the circulation due to previous formation through unknown mechanisms binds to these ANCA antigens on the surface eading to neutrophil activation and interaction with including reactive oxygen species, PR3 and MPO, and other granule enzymes cause endothelial cell apoptosis and necrosis, leading to endothelial injury

## Infections associated with vasculitis are:

- Bacterial Neisseria.
- Rickettsial RMSF.
- Spirochetes Syphilis.
- Fungai Aspergillus / Mucor.
- Viral Varicella.

Non infectious vasculitis.

#### Classification:

Immune complex mediated - SLE, Drug induced, Viral (HBSAg, HCV, RNA).

ANCA associated - cANCA seen with Wagener's granulomatosis.

PANCA seen with microscopic polyangiitis and Churg Strauss syndrome.

Anti endothelial antibodies – Kawasaki's.

Anti endothelial antibodies		Mediu	m sized '	vessels	Charac
	arteritis)	Polyarteritis disease.	nodosa	Kawasakı's	Wegener's granulomatosis Churg Strauss.  Microscopic polyarteritis. Henoch Schonlein purpura. Essential cryoglobulinemia.

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170	A service de la constantina	D. C.
Large-Vessel Vasculitis	Giant-Cell (Temporal) Arteritis.	Granulomatous Inflammation; Frequently Involves The Temporal Artery. Usually Occurs In Patients Older Than Age 50 And Is Associated With Polymyalgia Rheumatica
Aorta And Large Branches To Extremities, Head, And	Taka) asu Arteritis	Granulomatous Inflammation Usually Occurring In Patients Younger Than Age 50.
Neck.		Necrotizing Inflammation Typically Involving Renal
Medium-Vessel Vasculitis	Polyarteritis Nodosa	Arteries But Sparing Pulmonary Vessels.
Main Visceral Arteries And Their Branches	Kawasaki Disease	Arteritis With Mucocutaneous Lymph Node Syndrome Usually Occurs In Children. Coronary Arteries Can Be Involved With Aneurysm Formation And/Or Thrombosis
Small-Vessel Vasculitis	Wegener Granulomatosis.	Granulomatous Inflammation Involving The Respiratory Tract And Necrotizing Vasculitis Affecting Small Vessels Including Glomerular Vessels. Associated With Pr3- Ancas.
Arterioles, Venules, Capillaries, And Occasionally Small Arteries	Churg-Strauss Syndrome	Eosinophil-Rich Granulomatous Inflammation Involved The Respiratory Tract And Necrotizing Vasculitis Affecting Small Vessels. Associated With Asthma And Blood Eosinophilia. Associated With Mpo-Ancas.
Tueries	Microscopic Polyanguitis	Necrotizing Small-Vessel Vasculitis With Few Or No Immune Deposits; Necrotizing Arteritis Of Small And Medium-Sized Arteries Can Occur. Necrotizing Glomerulonephritis And Pulmonary Capillaritis Are Common. Associated With Mpo-Ancas.

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#### Giant Cell arteritis:

#### **Most Common:**

- Granulomatous inflammation of aorta and major branches with a predilection for the extra cranial branches of carotid artery. Often involves the temporal artery.
- Seen in patients older than 50 years.
- Associated with polymyalgia rheumatica. Hematological malignancies appear in 2 to 4% of those with concurrent polymyalgia rheumatica.
- Unknown etiology.
- Giant cells seen in 2/3 of cases.
- Clinically Female > 50 years with history of fever and weight loss, c/o severe unilateral head ache with transient to permanent vision loss. ESR is markedly elevated.
- Diagnosis is by biopsy.

### Takayasu's arteritis:

- Granulomatous vasculitis of aorta and its major branches.
- · Occurs below 40 years.



- Classically involves aortic arch and pulmonary vessels.
- . Also called PULSELESS disease or REVERSE COARCTATION.

## Classical PAN:

- Necrotising arteritis affecting small and medium sized muscular arteries, esp renal arteries. Arterioles, capillaries and venules are spared. No Glomerulonephritis seen. Commonest sites are kidney, heart, liver, GIT, pancreas. Pulmonary vessels are spared. Vessels show irregular aneurismal dilatation, nodularity and obstruction.
- Transmural inflammation of arterial wall is seen with fibrinoid necrosis. Fibrosis may occur later. No granulomas seen. Lesions are in different staged, acute, healing and healed.
- PANCA associated

## Kawasaki's disease:

- Arteritis involving large, medium and small sized arteries.
- . Coronary arteries are often involved
- · Occurs in children. 80% cases occur below 4 years.
- · Cause of acquired heart disease in children.
- Associated with mucocutaneous lymph node syndrome.
- Due to anti-endothelial and anti-smooth muscle antibodies. May be virally triggered. Vessels show Tran mural inflammation with less prominent necrosis and no granulomas.

## Wegener's granulomatosis:

- Triad of
- Acute necrotizing granulomas in respiratory tract.
- Focal necrotizing or granulomatous vasculitis.
- Focal or diffuse necrotizing Crescentric Glomerulonephritis.
- Vasculitis affects capillaries, venules and arterioles and also small and medium sized arteries most prominent in the upper airways and lungs.
- Peak incidence in fifth decade.
- CANCA associated in up to 90% patients and is a good marker of activity.

## Churg Strauss syndrome:

- Also called allergic granulomatosis and angiitis.
- Lesions are identical to PAN. Seen to involve small to medium sized vessels.
- Strong association with bronchial asthma, allergic rhinitis and eosinophilia.
- Pulmonary and splenic veins and peripheral nerves are frequently involved with intra and extravascular granulomas and eosinophilic infiltration.
- Renal disease is infrequent.
- PANCA is seen in 70% cases.

## Microscopic polyangiitis:

- Also called Leukocytoclastic / hypersen- sitivity vascultits or microscopic polyarteritis.
- Necrotizing vasculitis affecting small vessels esp of skin and mucous membranes.



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leukocytoclastic with palpable Isolated Cutaneous vasculitis presents

Necrotising arteritis of small and medium arter es, necrot zing Giomerulonephritis and pulmonary capillaritis is common.

 Sites involved are skin, mucous membranes lung, brain, heart, GIT, Kidney, muscles.

Associated with p ANCA in 80% cases.

 Pauci immone lesions with no immune deposits. Leukocytoclasia is seen.

 Disseminated vascular lesions of hypersensitivity anglitis may also appear in a number oil syndromes including Henoch Schonlein purpura, Essential cryoglobulinemia, vasculitis with connective tissue disorders and malignancies.

## Henoch Schonlein purpura:

Vasculitis with IgA dominant immune deposits affecting small vessels typically of skin, gut and glomeruli. Associated with arthritis and arthralgias.

## Essential cryoglobulinemia:

Cryoglobulin deposits in vessels along with cryoglobulins in serum. Skin and glomeruli often involved.

### Buerger's disease:

- · Also called thromboanglitis obliterans.
- Segmental thrombosing acute and chronic inflammation of medium and small arteries. Associated with smoking
- Affects tibial and radial arteries most often.
- Histologically shows thrombus with abscesses and granulomatous reaction with acute and chronic inflammation of wall.

#### Aneurysm:

Localized abnormal dilatation of blood

True- bounded by complete arterial waii components.

False - or pseudoaneurysm is haematoma communicating with the vessel lumen Dissecting aneurysms are false aneurysms

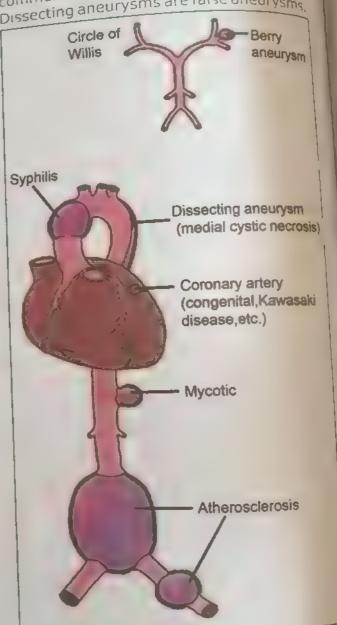


Fig. 7.7: The locations of aneurysms. Syphilitic aneurysms are the common variety in the ascending aorta, which is usually speared by the atherosclerotic process. Atherosclerotic aneurysms can occur in the abdominal aorta or muscular arteries including the coronary and popliteal artenes and other vessels Berry aneurysms are seen in the circle of Willis

mainly at branch points; their rupture leads to subarachnoid hemorrhage. Mycotic aneurysms occur almost anywhere that bacteria can deposit on vessel walls



Aortic aneurysm:

Most frequently due to atherosclerosis. Other causes are cystic medial degeneration, Syphilis, trauma.

Arter al aneurysms are due to vasculitides, trauma or congenital (Berry).

Aneurysms are fusiform, cylindroid or saccular.

Commonest site atherosclerotic aneurysm is abdominal aorta below renal arteries and above iliac bifurcation. Other sites are common iliac, descending thoracic aorta and arch of aorta. Until proved otherwise an abdominal aneurysm is assumed to be atherosclerotic in origin.

Syphilitic aneurysms:

- · (Luetic aneurysm) are seen in tertiary syphilis. Involve ascending aorta.
- Due to obliterative endarteritis of vasa vasora.
- Tree barking appearance is linear wrinkled appearance of intimal surface.
- Lead to aortic regurgitation and dilated heart called cor bovinum.

Dissecting aneurysms:

- · Are due to dissection of blood between and along laminar planes of media (Intra mural haematoma). Dissections almost always originate with intimaltears. 90% located within 10cms of aortic valve. Blood propagates between outer + middle third of media.
- 40-60 years Associated with hypertension.
- Younger patients Associated with Marfan's syndrome.
- Type I + II Ascending aorta (Type A) Type III- Descending aorta (Type B).
- Histologically detectable lesion is cystic medial degeneration, characterized by elastic tissue fragmentation with separation by small cleft like spaces filled with amorphous EMC. This change is seen in Marfan's.
- Annulo aortic ectasia is also seen in Marfans.

#### Veins:

Commonest site of varicose veins

Superficial veins of legs.

Thrombosis

- Deep Veins of lower extremities.

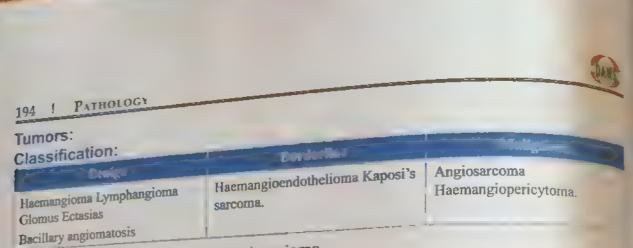
S.V.C. Syndrome

- Bronchogenic C<sub>A</sub> Mediastinal lymphoma

IVC Syndrome

- Hepatocellular CA

Renal cell C<sub>A</sub> Milroy's Disease = Heredofamilial congenital lymphodema.



Chapter

EXTRA

Cystic hygroma - Cavemous lymmphangioma.

Glomus - Commonest site is distal digits, esp sub ungula location. Tumor of neuromyoarterial receptor cells.

Pyogenic Granuloma – Lobular capillary haemangioma. Granuloma gravid arum of pregnancy commonly located in the gums is this type of tumor.

Nevus flammeus - Salmon patch and port wine stain.

#### **Bacillary angiomatosis:**

Associated with AIDS.

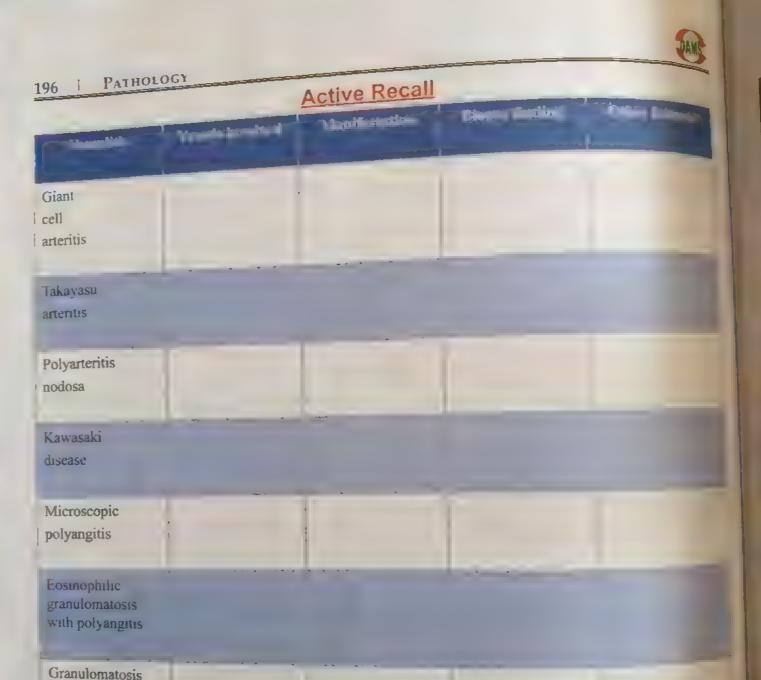
Opportunistic infection due to Bartonella henslae, a gram negative bacillus causing cat scratch disease.

Shows reactive vascular proliferation with epithelioid endothelial cells, nuclear dust, neutrophils and granular material which is the causative organism.

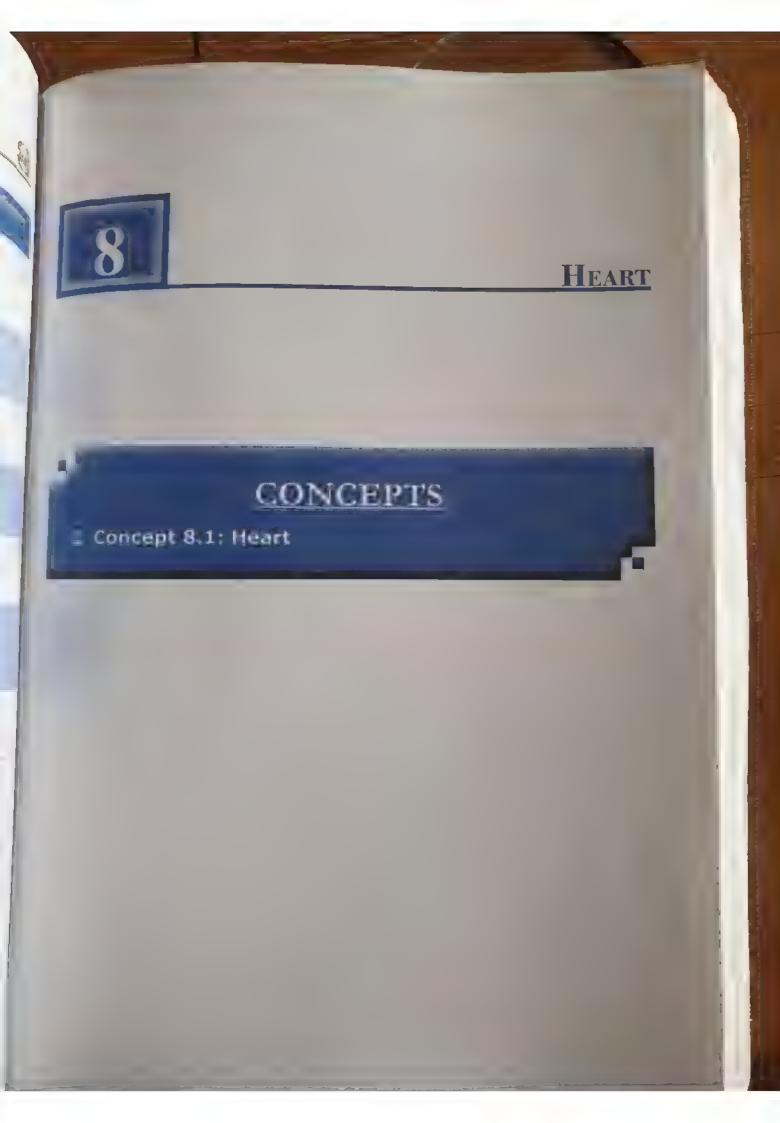
Cat is reservoir and flea is vector. Erythromycin and macrolide antibiotics are effective. Kaposi's sarcoma - Commonest AIDS associated neoplasm.

### Fibromuscular Dysplasia

- Focal irregular thickening of the walls of medium and large muscular arteries, including renal, carotid, splanchnic, and vertebral vessels.
- The cause is unknown but is probably developmental; first-degree relatives of affected individuals have an increased incidence.
- Segments of the vessel wall are focally thickened by a combination of irregular medial and intimal hyperplasia and fibrosis; this results in luminal stenosis, and in the renal arteries may be a cause of renovascular hypertension.
- Vascular outpouchings (aneurysms) may develop in the vessel segments with attenuated media and in some cases can rupture.
- Fibromuscular dysplasia can manifest at any age, although it is seen most frequently in young women: there is no association and age, although it is seen most frequently in the second state. young women; there is no association with use of oral contraceptives or abnormalities



with polyangitis



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Concept 8.1: Heart

Learning Objectives: Myocardial infarction gross and histology, vegetations, rheumat,

heart disease, cardiomyopathies

## Time Needed

The state of the s	1 hours
1° reading	25 mins
2m reading	

Cardiac hypertrophy.

Hypertrophy of heart is due to volume overload causes eccentric hypertrophy.

Volume overload causes eccentric hypertrophy. Hypertrophy of heart is use to volume overload causes eccentric hypertrophy. leads to concentric hypertrophy. leads to concentric hypertrophy. Volume diate early genes and fetal gene programming Hypertrophy involved re-induction of immediate early genes and fetal gene programming

Mild - pulmonary hypertension, IHD 2 times. Moderate - hypertension, Aortic stenosis, MR, DCM 2-3 times.

Severe - AR, HCM Greater than 3 times.

## Causes of Left sided Heart Failure:

- 1. IHD.
- 2. Hypertension.
- Aortic valvular disease + MR (RHD + Mitral prolapse).
- 4. 1° myocardial disease.

LUNGS- Pulmonary edema, CVC lung - Hear failure cells + brown induration of lungs dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and cough - frothy + blood tinged sputum.

KIDNEYS - Pre renal azotemia. CEREBRAL - Hypoxia - irritability + restlessness.

## Causes of Right sided Heart Failure:

- 1. MS.
- Left to right shunts.
- 3. Intrinsic disease of lung or pulm. Vasculations -↑ resistance in pulmonary circulation + Cor Pulmonale.
- 4. Less commonly cardiomyopathy + myocarditis.

Diseases of Lung - COPD, Diffuse pulmonary interstitial fibrosis, extensive persistent atelectasis.

Cystic fibrosis.

Diseases of Pulmonary vessels – Pulmonary embolism, 1° pulmonary vascular scierosis. Extensive pulmonary arteritis (WG), Drugs + toxin induced vasc sclerosis.

Disorders affecting chest movement

Kyphoscoliosis marked obesity = Pick Wickian Syndrome neuromuscular disorders. Disorder inducing pulmonary arteriolar constriction- chronic altitude sickness, obstruction to major airways, idiopathic alveolar hypoventilation.

LIVER - Nutmeg Liver

SPLEEN - Congestive splenomegaly

KIDNE - More pronounced pre-renal azotemia

Peripheral edema and effusions.

Ischaem Also called

resulting proven ot Four isch Angir

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## Ischaemic Heart Disease:

AISO called Coronary artery disease. Critical factor is reduction in coronary blood flow Also cancer in insufficiency of oxygen and nutrients and accumulation of metabolites. Until resulting the re Four ischemic syndromes are:

1. Angina pectoris. 2. Myocardial infarction.

3. Chronic ischemic heart disease.

4. Sudden cardiac death - Death within 1 hour from cardiac causes.

Pathogenesis:

A. Role of fixed coronary obstruction - 90% cases of IHD have fixed critical (> 75% of cross section) obstruction of at least one major epicardial artery.

B. Role of acute plaque change-Hemorrhage/ rupture of fissuring /erosion or ulceration of plaque triggers thrombosis.

Disrupted plaque is markedly eccentric, with large soft core of necrotic debris and lipid high density of macrophages and a thin fibrous cap.

. Role of coronary thrombosis - Critical role in acute coronary syndromes. In MIcomplete stenosis due to thrombosis. In Unstable angina, there is transient mural thrombosis.

D. Role of vasoconstriction - Transient vasospasm is induced at the site of plaque disruption and thrombosis.

disrupcion and	
A Stable angina	Fixed critical stenosis.
B Unstable angina	Plaque rupture with mural thrombus, often with thromboemboli, with vasoconstriction leading to decreased coronary flow.
( MI	Plaque rupture with complete thrombosis.
D Sudden death	Severe multivessel disease, often plaque rupture, often thrombus or thromboemboli, triggering a fatal arrhythmia.

Sudden cardiac death - Is most commonly due to IHD. Ultimate mechanism is development of fatal arrhythmias. Others causes are aortic valve stenosis, abnormalities of conduction system, mitral valve prolapse, myocarditis and dilated or Hypertrophic cardiomyopathies.

Chronic ischemic heart disease - Is used for patients who develop insidious CHF as a consequence of IHD. Also called ischemic cardiomyopathy OR atherosclerotic coronary artery and ischemic heart disease with heart failure.

Angina pectoris - is paroxysmal attacks of chest discomfort caused by transient Ischemia that falls short of inducing infarction.

### Types:

- Stable angina ischemia induced by increased demand. Pain is relieved by rest ECG shows ST depression. Due to Fixed coronary obstruction
- Variant or Prinzmetal angina Pain is present at rest. Due to coronary artery spasm Relieved by vasodilators. ECG shows ST elevation.



• Unstable / Crescendo /Preinfarction angina – pain occurs with progressive, Unstable / Crescendo /Preimarcuoli angula with acute plaque change in a progressive, progressive ncreasing frequency and less effort. Association and aggregation are important in preexisting coronary thrombus. Platelet activation and aggregation are important in its pathogenesis.

## Mycoardial Infarction:

Infarcts can be transmural or Subendocardial.

Transmural infarcts involve full thickness of myocardium and are associated with coronary atherosclerosis, plaque rupture/ fissure/ sudden change in morphology with activation of coagulation leading to occlusive thrombosis.

Subendocardial infarcts involve inner 1/3 to 1/2 of wall. Are associated with diffuse stenosing coronary atherosclerosis with reduction in blood flow. No plaque rupture or thrombosis is seen. 10% Infarcts seen without coronary atherosclerosis- Due to Vasospasm and platelet aggregation, Emboli from mural thrombus or vegetative endocarditis / Paradoxical emboli, No abnormality seen an angiography in one third of these cases.

### Myocardial response to ischemia:

Ischemia is most pronounced in the sub endocardium.

## Approximate Time of Onset of Key Events in Ischemic Cardiac My

Feature	y and in isomethic Call	ulac wyocytes
	Line	
Onset of ATP depletion	Seconds	
Less of cortract.hty	The section was a	
AIP reduced	<2 min	
to 50° of normal		
to 10% of normal	10 min	_
Irreversible ce Linjury	40 min	
Microvascular injury	20 40 min	-
and the same of the same	>1 hr	
	The state of the s	



# orphologic Changes in Myocardial Infarction

lution	of Morphologic	Changes in Myocardial Infarction Light Microscope	Fiegiron
) Ratio	Gross Fegures	Light vitetoscupe	Microscope
eversible l	None	None	Relaxation of myofibrils; glycogen loss; mitochondrial swelling.
<sub>reversible</sub>	Injury.	- Charact	Sarcolemnial
1 hr	Nane	Usually none; variable waviness of fibers at border.	disruption; mitochondrial amorphous densities
י זר	Dark mottling (occasional).	Early coagulation necrosis; edema: hemorrhage.	
	Dark mottling	Ongoing coagulation necrosis, pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; early neutrophilic infiltrate.	
3 days	Mottling with yellow-tan infarct center.	Coagulation necrosis, with loss of nuclei and striations; brisk interstitial infiltrate of neutrophils.	
	Hyperemic border; central yellow-tan sottening.	Beginning disintegration of dead myofibers. with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border.	
10 days	Maximally yellow- tan and soft, with depressed red-tan	Well-developed phagocytosis of dead cells; early formation of fibrovascular granulation tissue at margins.	
16. j.4 duys	Red-gray depressed	Well-established granulation tissue with new blood vessels and collagen deposition.	
2-8 wk	Gray-white scar, progressive from border toward core of infarct.	Increased collagen deposition, with de- creased cellularity.	
2 m ,	Scarring complete	Dense collagenous scar.	

Fig. 8.1: Development of a myocardial infarct. A. Normal myocardium. B. After about 12 to 18 hours, the infarcted myocardium shown eosinophilia (red staining) in section of the heart stained with hematoxylin, and at the periphery of the infarct. D. After about 3 weeks, peripheral portions of the infarct are composed of has been largely removed from this area, and a small amount of collagen has been laid down. E. after 3 months or more, the infarcted region has been replaced by scar tissue.

Contraction band necrosis represents reperfusion injury. They are intensely eosinophilic transverse bands that traverse the involved myocyte. Due to hyper contraction of myofibrils in the dying cell.

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Fig. 8.2: Contraction band necrosis: A section of infarcted myocardium shows prominent thick, wavy, transverse bands in myofibers.

Stunned myocardium is prolonged post ischemic ventricular dysfunction in the reperfused myocardium.

### Complications of MI are:

- Sudden cardiac death in 20% patients.
- No complication in 10-20% patients.
- Complications in 80-90% cases which include.
  - Cardiac arrhythmias (Commonest).
  - LVF with pulmonary edema.
  - · Cardiogenic shock.
  - Thromboembolism.
  - Cardia rupture syndromes (due to weakening of the necrotic myocardium) which include.
- Rupture of the ventricular free wall with heamopericardium and cardiac tamponade (commonest).
- Rupture of interventricular septum leading to Left to right shunt.
- Papillary muscle rupture leading to severe MR.
  - Fibrinous or fibrinohaemorrhagic pericarditis.
  - Ventricular aneurysm is a late complication mostly following a large anteroseptal transmural infarct.

Pericarditis, cardiac rupture and ventricular aneurysms rarely develop after sub endocardial infarcts.

#### Hypertensive Heart Disease:

Left sided concentric hypertrophy seen in pressure overload. Wall thickness more than 2 cm and weight more than 500 grams.

## Acute cor pulmonale is seen after massive pulmonary embolism.

Chronic cor pulmonale is seen due to prolonged pressure over load in lung / vessel / chest wall diseases.

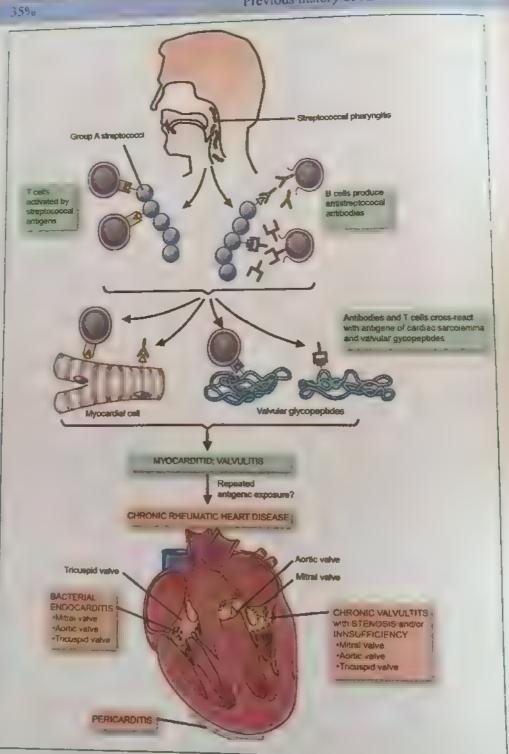


## Rheumatic Heart Disease:

Jones Criteria

2 major or 1 major + 2 minor

Z inajor of a s	Minor
Major.	Arthralgia - Fever
1. Polyarthritis-75%	Previous history of RF
2 Carditis 35%	[1011000



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Fig. 8.3



Rheumatic carditis - Pancarditis. Endocarditis - Mitral valve above 75%; Mitral + Aortic - 25%.

- Vegetations along line of closure, which are verrucous, sterile and small.
  - Mc callum's patch- commonest in post wall of left atria.
  - . MR, Chronic fish mouth / button

  - Myocarditis Aschoff bodies are diagnostic non caseating fibrinoid necrosis surrounded by Anitschkow myoocytes (caterpillar cells), Aschoff's giant cells, mononuclear cells + fibroblasts.
  - Pericarditis Fibrinous; Bread + Butter appearance.

In Acute Rheumatic fever, Myocarditis is most dangerous.

In chronic RHD, Endocardial and valvular involvement dominate.

## Infective Endocarditis:

May be Bacterial, Fungal, Rickettsia or Chlamydial.

predisposing factors are preexisting cardiac abnormalities like congenital HD< Damaged valves, neutropenia, immunodeficiency, indwelling vascular catheters, diabetes mellitus, alcohol, intravenous drug abuse.

Organisms- Strept viridans, Staph aureus (commonest cause of acute endocarditis and endocarditis in drug abusers), Strept pneumoniae, gram negative rods, fungi.

Acute Bacterial endocarditis occurs in normal valves due to high virulence organisms

Sub - acute Bacterial endocarditis is due to organisms of low virulence affecting previously damaged valves and is a more treatable condition.

Vegetations are bulky, friable, and destructive and composed of fibrin, inflammatory cells and microorganisms.

## Complications of IE include.

- 1. Cardiac.
- 2. Embolic.
- 3. Renal.

#### Cardiac include.

- Valvular insufficiency / stenosis and
- failure.
- Myocardial ring abscess, perforation of aorta / heart.
- Suppurative pericarditis.
- Partial dehiscence of artificial walls.

Embolic phenomena result in abscess / infarcts.

- To brain, kidney and spleen in left sided lesions.
- To lungs in right sided lesions.

## Renal complications include.

- Focal Glomerulonephritis.
- Diffuse glomerulonephritis.
- Multiple abscesses.
- Embolic infarction.

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Non bacterial thrombotic endocarditis Marantic endocarditis, occurs in debilitated patients.

Vegetations are small sterile masses of fibrin and blood elements on normal valves

Vegetations are small sterile masses of fibrin and blood elements on normal valves

No organisms seen, lesions are non destructive. No organisms seen, lesions are non destructive.

No organisms seen, lesions are non destructive.

Associated with hypercoagulable states, mucinous adenocarcinomas of pancreas. Gly

Associated Victorian Catheters. and ovary, Indwelling Catheters.

Libman Sach's endocarditis

Associated with SLE.

Vegetations are small sterile 1-4 mm on either side of valve leaflets, most frequent in

the undersurface of AV valve. Associated with vasculitis. Haematoxylin bodies may be seen.

Divided into Cardiomyopathies and Specific heart muscle diseases.

Cardiomyopathy and Indirect Myocardial Dysfunction: Functional Patterns

and Cause		inisms .	Causes of Phenotype.	Indirect Myoc;  Discussion  Cardiomyon:thy)
Dilated	<40%	Impairment of contractility (systolic dysfunction).	Genetic; alcohol; peripartum; myocarditis; hemochromatosis; chronic anemia; doxorubicin (Adriamycin); sarcoidosis; idiopathic.	Ischemic heart disease; valvular heart disease; hypertensive heart disease; congenital heart disease.
Hypertrophic	50% to 80%	Impairment of compliance (diastolic dysfunction).	Genetic; Friedreich ataxia; storage diseases; infants of diabetic mother.	Hypertensive heart disease; aortic stenosis.
Restrictive	45% to 90%	Impairment of compliance (diastolic dysfunction).	Amyloidosis; radiation- induced fibrosis; idiopathic.	Pericardial construction.

#### DCM:

- Seen with infective myocarditis, Haemochromatosis, Chronic anemia, Alcoholism, Adriamycin toxicity, Sarcoidosis.
- Systolic failure.
- Hear is enlarged 2-3 times and is flabby. Chambers are dilated. Thickness of left ventricle is <,  $\simeq$  or > normal.

#### HCM:

 Associated with Friedrich's Ataxia. Glycogen storage disease, Infants of diabetic mothers, Hypertensive heart disease.

Diastoli

Heavy, mid ve

RCM: seen Diast Norm

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- Diastolic failure.
- . Heavy, muscular hyper contracting heart. Commonest site is sub aortic followed by mid ventricular. Histology shows myofiber disarray.

#### RCM:

- Seen in amyloidosis, radiation associated fibrosis.
- Diastolic failure due to impaired diastolic relaxation.
- Normal sized ventricles. Patchy or diffuse interstitial fibrosis

# Specific Heart Muscle Disease:

Myocarditis: Inflammation of the heart muscle with leukocyte infiltration and non ischemic necrosis of myositis. Leads to heart failure with fever and sudden appearance of ECG changes.

## Commonest cause is viral (Coxsackie B virus):

#### Idiopathic

#### Infectious

1 n.

Part.

· Viral. Coxsackievirus, adenovirus, echovirus, influenza virus, human immunodeficiency virus and many others.

Rickettsia. Typhus, Rocky Mountain spotted fever.

Bacterial: Diphtheria, staphylococcal, streptococcal, meningococcal, Borrelia (Lyme disease) and leptospiral infection

Fungi and protozoan parasites: Chagas disease, toxoplasmosis, aspergillosis, cryptococcal and candidal

Metazoan parasites: Echinococcus, Trichina.

#### Noninfectious.

- Hypersensitivity and immunologically related diseases: Rheumatic fever, systemic lupus erythematosus, scleroderma, drug reaction (e.g.to penicillin or sulfonamide) and rheuma-toid arthritis.
- Radiation.
- Miscellaneous: Sarcoidosis, uremia.

#### Pericardial Disease:

Pericarditis is inflammation of the pericardium. Causes are

- Infections Virus, Pyogenic bacteria, TB, Fungi, Bacteria.
- Immunologic Rheumatic fever, SLE, Scleroderma, Post cardiotomy, Dressler's syndrome, Drug hypersensitivity.
- Miscellaneous Post MI, Uraemia, Post surgical, Neoplastic, Traumatic, Post irradiation.
- Types are Acute.
  - Serous Non infectious inflammation, RF, SLE, Scleroderma, Tumours, / Uraemia, Viral.



EXTRA PO

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- Serofibrinous / Fibrinous MOST
- FREQUENT FORM. Acute MI, Post MI, Post Surg cal and later stage of Serous.

- Haemorrhag c MOST COMMONLY Tubercular. Other causes are Neoplas a Or Puru ent - Infect.ve organisms.
- Caseous Tubercular or mycobacterial infections.
- Healed Fo lows suppurative, caseous, surgery and irradiation. Healed - Fo lows suppurative, Lascous,
   Adnesive pericarditis and mediastinopericarditis. Thin strands of fibrosis obliterating
   Adnesive pericarditis and mediastinopericarditis. DCM like heart.
- per cardia. sac and adhering it to the mediastinum. DCM like heart. per cardia, sac and admerting it to the adense fibrous calcific scar which limits

  Constrictive pericarditis – Encased in a dense fibrous calcific scar which limits
- diastolic expansion. Quiet heart with reduced output.
- Most common heart finding in Rheumatoid arthritis is fibrinous pericarditis.

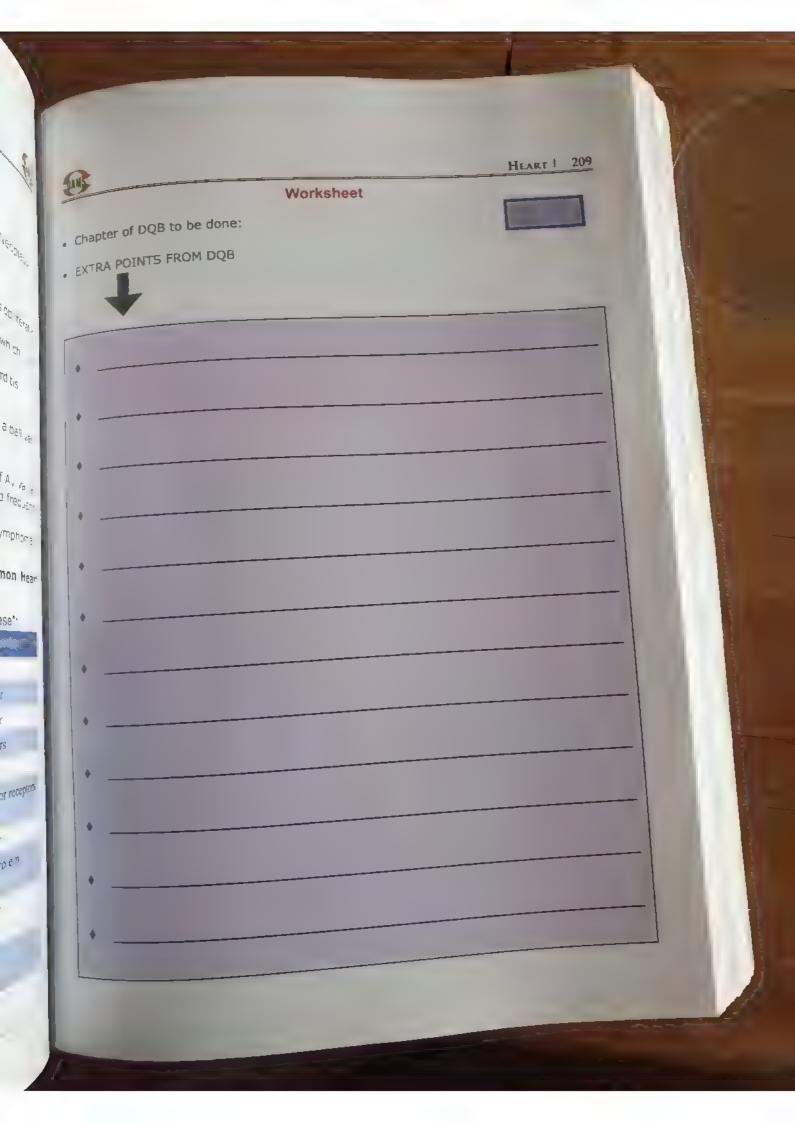
- Myxoma- Commonest, In Left atrium (Fossa ovalis), Obstructs out flow in a ball valve fashion
- Lipoma Most often in left ventricle
- Papillary fibroelastoma- Incidental finding on Valves and Atrial surfaces of AV valves
- Rhabdomyoma Most frequent in infants. Contain Spider cells. Increased frequency in Tuberous sclerosis.
- Secondary Most common from Lung, Breast, melanoma, Leukemias, Lymphomas.

## Most Common Tumor of Heart: Secondaries.

Most Common Heart Tumor of Infants: Rhabdomyoma. Most Common Heart Tumor of Adults: Myxoma.

Selected Examples of Gene Defects Associated With Congenital Heart Disease\*:

Selected Examples of Gene Defects Associated With Congenital Heart Disease.				
Charles and the same of the sa				
Nonsyndromic				
ASD or conduction defects	NKX2 5	Transcription factor		
AND or VND	GATA4	Transcript on factor		
Tetra.ogy et Fallot	ZFPM2 or N 012.5	Transcription factors		
Syndrom.e.				
Alagille syndrome – pulmonary artery stenosis or tetralogy of Fallot	JAG1 or N0TCH2	Signaling proteins or receptors		
Char syndrome = P[)A	TFAP2B	Transcription factor		
CHARGE syndrome ASD, VSD, PDA, or hypoplastic right side of the neart	GHD7	Helicase-binding protein		
DIGeorge syndrome ASD, VSD, or outflow tract obstruction	TBX1	Transcription factor		
Holt-Oram syndrome ASD, VSD, or conduction defect	TBX5	Transcript on factor		
Noonan syndrome pulmonary, valve stenosis vsd, or hypertrophic cardiomyopathy	PTPN11 KRAS, S0S1	Signaling proteins		



# HEPATOBILIARY SYSTEM

# CONCEPTS

Concept 9.1: Hepatobiliary System

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Concept 9.1: Hepatobiliary System Concept 9.1: Hepatobiliary System

Learning Objectives: Cirrhosis, histology of viral hepatitis, Wilson's Disease

hemochromatosis, tumors

# Time Needed

1000	1.5 hours
1ª reading	45 mins
2 <sup>nd</sup> reading	

# Liver & Gall Bladder:

Weight: 1400-1600gm 2.5% of Body weights.

Incoming blood.

- Portal vein (60-70%).
- Hepatic artery (30%-40%).

Outgoing- Hepatic vein  $\rightarrow$  IVC.

### Microanatomy:

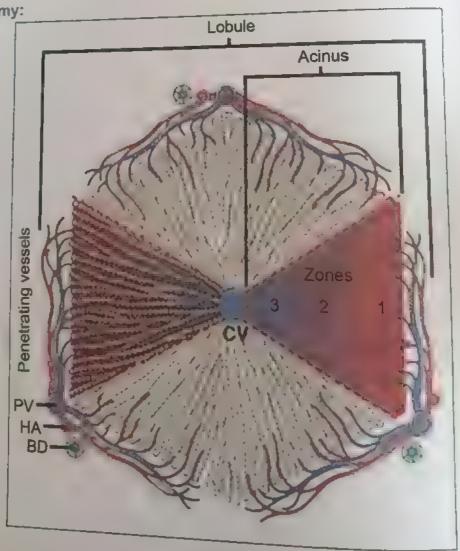


Fig. 9,1

Microscop acinar mo periphery and centr can be de the farthe

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Fatty I Causes

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Microscopic anatomy of the liver; the two models, hepatic lobular model and Microscopial are illustrated. In the lobular model the terminal hepatic main (CV) is at the center of a "lobule," while the portal tracts (PV) are at the periphery. Pathologists refer to the regions of the parenchyma as "periportal periphery and centrilobular." In the acinar model, on the basis of blood flow, three zones can be defined, zone 1 being the closest to the blood supply and zone 3 being the farthest. BD, bile duct; HA, hepatic artery.

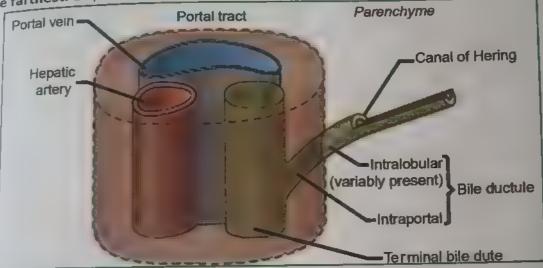


Fig 9.2. Schematic diagram of relationship between bile ducts, ductules and canals of Hering.

### Fatty Liver:

Causes of fatly changes in liver.

- DM.
- Alcoholism (Most Common).
- Anoxia,
- Toxins- CCI.

Drugs: Corticosteroids, salicylates tetracyclines, Na Valproate.

- Starvation.
- Obesity.
- Chronic illness.
- Acute fatly liver of pregnancy.
- Reyes syndrome.
- chronic HCV infection.

CC1<sub>4</sub> & Protein malnutrition: \$\preceq\$ synthesis of Apo protein, drugs: Corticosteroids salicylates tetracyclines Na Valproate ↓ FA oxidation.

Alcohol- shunting of (n) substances away from catabolism & towards lipid biosynthesis (because of 1 NADH).

- Impaired assembly & secretion of Lipoproteins due to Apo protein deficiency.
- Increased peripheral catabolism of fat.

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Jaundice: Elevated serum bilirubin (>2mg/di)

- Excessive production of bilirubin
- Reduced hepatocyte uptake
- Impaired bilirubin conjugation
- Decrease hepatocellular excretion
- Impaired bile flow

Unconjugated hyperbilirubinema

Conjugated Hyper bilirubinemia

# Causes of Jaundice:

# 1. Predominantly Unconjugated Hyperbilirubinemia.

# Excess production of bilirubin.

- Hemolytic anemias.
- Resorption of blood from internal hemorrhage (e.g. alimentary tract bleeding)
- Ineffective erythropoiesis syndromes (e.g. pernicious anemia, thalassemia).

## Reduced hepatic uptake:

- Drug interference with membrane carrier systems eg. rifampicin.
- Some cases of Gilbert syndrome.

# Impaired bilirubin conjugation:

- Physiologic jaundice of the newborn (decreased UGT1A1 activity, decreased excretion
- Breast milk jaundice (β- glucouronidases in milk).
- Genetic deficiency of UGT1A1 activity (Criggler Najar syndrome types I and II).
- Gilbert syndrome (mixed etiologies).
- Diffuse hepatocellular disease (e.g. viral or drug-induced hepatitis, cirrhosis).

# 2. Predominantly conjugated Hyperbilirubinemia:

- Deficiency of canalicular membrane transporters (Dubin- Johnson syndrome, Rotor syndrome).
- Impaired bile flow stone, stricture, carcinoma (surgical jaundice).
- 3. Neonatal Jaundice (physiological jaundice of newborn).
- Transient.
- Conjugating /excretory mechanism matures at 2 wks. of age.
- Breast milk contains β glucuronidase, which deconjugates bilirubin in intestine.

# 4. Hereditary hyperbilirubinaemias

# Unconjugated Hyperbilirubinemia:

- a. Criggler Najar syndrome Type I.
- AR.
- Absent UGT1A1 activity.
- · Fatal (within 19 months of birth).
- (N) Liver morphologically.

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- b. Criggler Najjar syndrome Type II.

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- UGIA1 less severe, non-fatal, activity (+).
- Liver (N).
- c. Gilbert's syndrome? AD.
- Benign; mild fluctuating hyper bilirubinemia.
- . UGTA1 activity (to 30% of (n).
- Liver (n) typically detected in adolescent / adult life in association with stress, strenuous exercise.
- . 6% of population.

# Conjugated hyper bilirubinemia:

# a. Dubin Johnson syndrome:

Impaired excretion of bilirubin glucoronides (canalicular membrane carrier protein MRP2 absent).

- Liver: Darkly pigmented (coarse pigmented granules within cytoplasm of hepatocytes).
- · Electron microscopy? Epinephrine metabolite in lysosomes.
- · Asymptomatic / chronic & recurrent jaundice.

### b. Rotor syndrome:

- · AR.
- Multiple defects in hepatic uptake and excretion of bilirubin.
- Liver (N).
- Jaundice, Asymptomatic.

### Cholestasis: Causes are:

- Hepatocellular dysfunction.
- Intrahepatic biliary obstruction.
- Extrahepatic biliary obstruction.

### C/F:

- 1. (Pruritus, skin xanthomas.
- 2.  $\uparrow$  S alkaline phosphates  $\uparrow$  Gamma- glutamyltranspeptidase,  $\uparrow$  5' nucleotidase).
- 3.  $\downarrow$  bile flow  $\Rightarrow$  malabsorption.

# Familial intrahepatic cholestasis 2 groups of disorders:

### Group I- Disorders with ↓ GGT.

- ↓ Bile salts and bile acids, ↓ cholesterol and ↓ phosphatidylcholine secretion in bile.
- ? S. bile acids pruritus.
  - TS. Cholesterol.
  - ↓ Gamma- glutomyl transpeptidase (GGT).
- a. Benign recurrent intrahepatic cholestasis
- Intermittent attack of cholestasis over life.
- No progression to chronic liver disease.



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- b. Progressive familial intra hepatic cholestasis 1 (PFIC-1).
- Cholestasis in infancy.
- Liver failure by adult hood.
   Also c.a byler syndrome (family members affected) or byler disease (unrelated) individuals).

  • Mutation in ATP8 B1 gene on chromosome 18q21 encodes canalicular P-type ATPase

  • Mutation in ATP8 B1 gene on chromosome 2 (PFIC-2)0
- c. Progressive familial intra hepatic cholestasis 2 (PFIC-2)0

- Cirrhosis by 1<sup>st</sup> decade of file.
   Mutation in canalicular bile salt export pump (BSEP) encoded by ABCB11 gene 0. chromosome 2q24.

# Group II - 1 SGGT levels.

- Progressive familial intrahepatic cholestasis 3 (PIFC-3).
- Mutation in ABC B4 gene on chromosome 7q21.
- Encodes MDR3- canalicular transport protein responsible for flipping phosphaticy choline from internal to external leaflet of canalicular membrane.
- No phosphatidylcholine in bile.

H/P: Bile in hepatocytes, canaliculi, kupffer cells.

- Feathery/ foamy degeneration (wispy appearance).
- Parenchymal destruction ⇒ Bile lakes obstruction ⇒ Bile stasis ↑ back pressure.
- Proliferation of duct epithelial cell ⇒ looping and reduplication ⇒ bile lakes.
- PT fibrosis ⇒ Biliary Cirrhosis.

(Bile stained cirrhotic liver).

Extrahepatic cholestasis curable by surgery, intrahepatic cholestasis requires liver transplant.

### **Hepatic Failure:**

80% - 90% of hepatic functional capacity loss.

### Causes:

- a. Massive hepatic necrosis: Fulminant viral hepatitis, drugs and chemicals (acetaminophen, halothane, ATT (Rifampicin, INH) MAO inhibitors, CCI, Amantia phailoides).
- b. Chronic Liver disease chronic hepatitis, cirrhosis.
- c. Hepatic dysfunction without overt necrosis: Reye syndrome, tetracylcline toxicity acute fatty liver of pregnancy.

### Clinical features:

- Jaundice.
- Hypoalbuminemia leads to peripheral edema.
- Fetor hepaticus- musty body odour due to mercaptans.
- Palmar Erythema.
- Hypogonadism impaired metabolism of estrogen.
- Gynaecomastia.
- Portal H.T.



Life threatening complications.

Multiple organ failure esp. lung and kidney.

- Coagulopathy due to impaired hepatic synthesis of factors II, VII, IX & X resulting in bleeding tendency.
- , Hepatic encephalopathy. EEG-n, specific, Asterixis- characteristic.
- . Cause- disorder of neurotransmission in the CNS and neuromuscular system due to 1 levels of ammonia that impairs neuronal function and promotes brain edema.
- , Hapatorenal Syndrome.
  - Renal failure in severe liver disease with no cause for renal failure.
- , Hepatocellular carcinoma:

### Cirrhosis:

Three character stics-

- . Bridging fibrous septae.
- Parenchymal Nodules.

3mm- Micronodular.

3 mm- Macronodular.

- Disruption of architecture ⇒ Abnormal vascular interconnection.
- Diffuse.
- Irreversible.

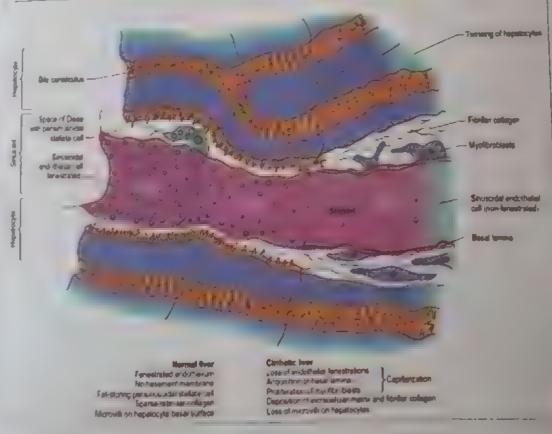
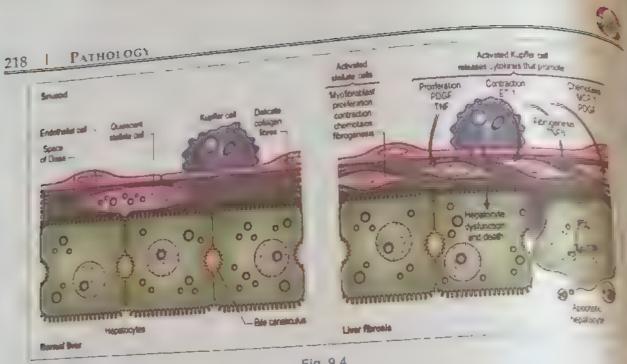


Fig 9.3



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Fig. 9.4

Regression in fibrosis is seen in:

- Schistosomiasis
- Hemochromatosis

### Causes:

- 1. Alcoholic liver disease- 60-70%.
- 2. Viral Hepatitis 10%.
- 3. Biliary Cirrhosis 5-10%.
- 4. Primary Hemochromatosis rare.
- 5. Wilson Diseased Rare.
- 6.  $\alpha$ -1 AT def Rare.
- 7. Drug induced a methyl dopa.
- 8. Cryptogenic 10-15%.

### Normally:

Type I & III (interstitial collagen - PT and around CVs.

Type IV - in space of Disse (alongside hepatocytes).

Cirrhosis - Type I and III collagen in lobules.

- Loss of (n) fenestrations in sinusoidal endothelial cells due to deposition of collagen in the space of Disse.
  - Source of collagen: Perisinusoidal hepatic stellate cells.
- · Transformed into 'myofibroblast like cells.

### Cause of death:

- Progressive Liver failure.
- Portal hypertension.
- Hepato cellular carcinoma.



# Infectious Disorders of Liver:

VIRAL HEPATITIS - caused by viruses having special affinity for liver; other viruses vIRAL HEPATISTICS (NEWBORN) like Epstein Barr virus. Cytomegalovirus (newborn/ immuno suppressed)

nepatinophic) like Epstein Barr virus. Cytomegalovirus (newborn/ immuno suppressed)

Call type	
Antigen-presenting cells Kupffer cells (KG) Dendritic cells (DC)	When activated, secrete TNF-n, IL-2, IL-12 and leukotriene B3 Express toll-like receptors (TLR); secrete IL-12, TIMF-m, IFN-m, and IL-10.
Scate immune system  Natural killer T cells (NKT)	'Pit cells'; can be Th-1* or Th-2**
Adaptive immune system  3. Amphocytes	Secrete immunoglobulin, generate plasma cells
Comphocytes  D4   I cells  D4   I be,per cells  D4   CD25   T cells  I-segs)	Multiple subsets Can be Th-1* or Th-2** Regulate activation of CD4+ and CD8+ T cells
in I ce ls tout I Cells (CTL)	Activity is enhanced by Th-1 cytokines; car be cytolytic or non-cytolytic.

h 2: anti-inflammatory, IL-4 and IL-10 secreting

Henat Ls A fHAV )	RIMA picornavirus  Sporadic or epidemic occurrence with faecal-oral transmission, resulting in acute disease only.
Fenatics Biff-EV)	DNA hepadnavirus  Sporadic or endemic occurrence through sexual, perinatal and parenteral transmission (hronic disease persists in 5% of aduits and in up to 90% of infants Chronic infection is associated with hepatocellular carcinoma.
Hepatitis ( (H( V)	RIMA flavi-like virus  Sporadic occurrence with parenteral transmission Perinatal and sexual spread is less common Chronic disease develops in 60-30% of persons infected and cirrhosis is associated with hepatocellular carcinoma.
Hepatitis D (HDV)	RIMA defective virus  Sporadic or endemic disease occurs as coinfection with HBV Transmission is purenteral and sexual Chronic disease is seen in patients with chronic HBV HDV worsens the clinical severity of HBV infection.
Hepatitis E (HEV)	RIMA virus  Sporadic or epidemic occurrence Transmission is faecal-oral, resulting in acut disease  Mortality rate is 25% in pregnant women.

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# 1. Hepatitis A Virus:

- Infections hepatitis, benign, self- limited disease.
  - IP: 2-6 weeks.
  - Chronic hepatitis None.
  - Carner state None.
  - Fulminant hepatitis Rarely.
- Worldwide, bod 11791010.
   Accounts for 25% of clinically evident cases of acute hepatitis world wide.
  - Unenveloped, SSRNA virus (Picorna virus) → Hepatovirus.

Spread: Feco-oral Route. In developed countries raw or steamed shell fish may Icosachedral capsid: 27mm in diameter

Present in stools: 2-3 weeks before and 1 week after onset of jaundice

 Serodiagnosis- IgM antibody appears in blood with onset of symptoms – marker of acute infection.

IgG antibody - lifelong immunity.

# 2. Hepatitis B Virus:

Serum Hepatitis.

- Acute hepatitis.
- Non –progressive chronic hepatitis → cirrhosis.
- · Fulminant hepatitis.
- Carrier state.
- Back drop for HDV infection.
- · HCC.

IP 30-180 days (1-6 months).

- HBV remains in blood: last stage of IP and Active disease (Acute and chronic).
- Present in all physiologic and pathologic body fluids, except in stools (unlike HAV).

MOI: Blood products, needle sticks etc. (30%).

- · Sexual transmission.
- Vertical → Carrier state.
- Belongs to Hepadnaviridae family.
- Spherical, double layered 'Dane particle' 42 mm in size.
- Core of virus contains double stranded DNA and enzyme DNA polymerase.

### Genome:

HBc Ag: Nucleo capsid core protein.

HBe Ag: Both precore and core region.

HBs Ag: Envelope glycoproteins Synthesized and secreted by infected hepatocytes. DNA polymerase that exhibits reverse transcriptase activity.

riBX: prote Transcrit Role in 1

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- HBX Protein form X region: Transcriptional transactivation of viral genes and host gene promoter.
- Role in HCC.

, phase of Infections:

proliferative Phase: HBV DNA in episomal form.

Formation of complete virion with associated antigens.

MHC c ass I  $\rightarrow$  CD8+ T cells activation  $\rightarrow$  Infected hepatocyte destruction.

- , Viral DNA incorporated into host DNA. Occurs in hepatocytes not destroyed by immune
- . With cessation of viral replication within hepatocytes and appearance of antibodies, infectivity ends and liver damage subsides.

# Serological Diagnosis:

### HBs Ag:

ŗ,

na li 11Kt \*\*

- Appears before onset of symptoms.
- . Peaks during overt disease.
- . 1 To undetected levels in 3-6 months.

# HBe Ag, HBV DNA, DNA polymerase appear:

- · After HBs Ag.
- Signify active viral replication.

### IgM Anti HBC:

- Appear shortly before onset of symptoms
- Concurrent with onset of ↑ S. aminotransferases.
- Marker of window period.
- IgM → IgG.

 Shortly after disappearance of HBe Ag (i.e. acute infection has peaked and disease is on its wane).

### Anti Hbs:

- Doesn't rise till acute disease is over.
- Not detectable for few weeks to several months after disappearance of HBs Ag (window period).
- Persists for life, conferring protection.

CARRIER STATE: HBs Ag>6 months (doesn't necessarily indicate replication)

- Persistence of circulating HBs Ag, HBV DNA usually with ant HBc and occasionally with anti Hbs.
- Progressive liver damage can occur.



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# 3. Hepatitis C Virus:

- MOI: Inoculation and Blood transitision → Infrequent causes: (risk of per.natal

   Sexual and vertical transmission → Infrequent causes: (risk of per.natal MOI: Inoculation and Blood transfusion
- Sexual and vertical transmission  $\rightarrow$  little control of per.natal transmission is much lower with hepatitis C-6% births to infected mother than transmission is much lower with hepatitis to infected mothers) with hepatitis B-20-60% of births to infected mothers) Most important Cause of transfusion associated hepatitis.
- Acute HCV infection is generally undetected clinically. Acute HCV infection is generally and curring and curring and curring in majority of infected individuals and currings.
   In contrast HBV, chronic disease occurs in majority of infected individuals and currings.
- Leading infectious cause of chronic Liver disease world wide. develops in 20% patients.

## Virus: Flaviviridae:

- · SSRNA.
- Unstable ⇒ Types and sub types.

Difficulty in vaccine development.

- ↑ IgG. Anti HCV → No effective immunity.
- Cirrhosis in 5-10 years.

### Serology:

IP: 2-26 weeks.

HCV RNA: present in blood for 1-3 weeks (with ↑ S. transaminase).

IgM Anti HCV → IgG Anti HCV.

Chronic infection: Episodic elevations in S. transminase with intervening (n) period. HCV RNA persists in blood.

### 4. Hepatitis D Viurs:

- Delta agent 35 nm SSRNA virus.
- Replication defective.
- Infection when encapsulated by HBs Ag
  - 1. Co-infection.
- Acute C- infection:
- Simultaneous exposure to HBV and HOV.
- HBV- must establish first,
  - Recovery 90%.
  - Fulminant Hepatitis: 3-4%.
  - Chronic Hepatitis: Rare.
- 1. Super Infection: In chronic carriers of HBV followed by, HDV infection. Disease after 3-50d.

Acute disease → Recovery: 10%-15%

Fulminant hepatitis  $\rightarrow$  7% - 10%

Chronic H8V/HDV hepatitis → 80%

### Serology:

HDVRNA+ in blood and liver just before and in early days of acute symptomatic disease IgM Anti HDV- most reliable marker (late and short lived)

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# 5. Hepatitis E Virus:

- Enterically transmitted.
- Sporadic infection.
  - Young middle age adults.
  - (Rare in children).
- Accounts for over 50% of cases of acute hepatitis in India.
- Pregnancy →high mortality (20%).
- . Self-limited (not associated with chronic disease).

IP: 2-8 weeks: not associated with persistent viremia & chronic liver disease Virus: SSRNA, Calciviridase unenveloped

Serology. HEV RNA & Virions + in stool & liver- before onset of clinical illness.

- ↑ 5. transaminases.
- , IgM anti HEV  $\rightarrow$  IgG (in 2-4 wks).

# 6. Hepatitis G Virus:

- . SSRNA.
- Flaviviridae.

MOI: Parenteral- Contaminated blood/ blood products.

- Possibly sexual. Prevalence of HGV RNA in blood donors 1-4%.
- In up to 75% of infections, HGV cleared from plasma, in remainder, infection becomes chronic.
- Site of HBV replication is mononuclear cells.
- No rise in S. amino transferases. Non- pathogenic.
- Co- infects patients with HIV, dual infection protective against HIV disease

# Clinico Pathologic Syndromes:

# A. Asymptomatic infections with recovery:

† S. transminase/presence of antiviral antibodies.

# B Acute viral Hepatitis: 4 phases.

### Phase:

- II. Symptomatic pre icteric phase. Non- specific, constitutional symptoms 10% have serum sickness like picture.
- III. Symptomatic icteric phase- Usual in adults with acute HAV (not children). Absent in about half cases of HBV and in majority of cases of HCV. Jaundice is predominantly conjugated hyperbilirubinemia.
- IV. Convalescence.

Peak infectivity: Last days of IP & early days of acute infection.

C. Chronic Viral Hepatitis: Symptomatic, Biochemical or serologic evidence of continuing or relapsing disease for > 6 months with histological documentation of

Etiology most important indicator of likelihood at progress to cirrhosis.

CARRIER STATE- Chronic hepatitis constitutes a "Carrier State". TATE- Chronic hepatitis constitutes without adverse clinical/ histologica

Healthy carrier - Harbor the virus without adverse clinical/ histologica Healthy Carrier Healthy Carriers with chronic liver disease but free of symptoms/ disability Carriers with symptoms of chronic disease

Early infection (Particularly vertical)  $\rightarrow$  90-95% Adult infection  $\rightarrow$  1-10%

# Old classification:

- Chronic Persistent Hepatitis (CPH).
- Chronic Active Hepatitis (CAH).
- Chronic Lobular Hepatitis (CLH).

CPH: In. in PT, no piecemeal necrosis.

CLH: Within Lobules.

Newer classification:

Etiology.
 Grading.
 Staging.

### Morphology:

HBV infection.

Ground glass hepatocytes → HbsAG in the form of spheres & tubules in cytoplasm. Sanded nuclei → HBc Ag in nucleus.

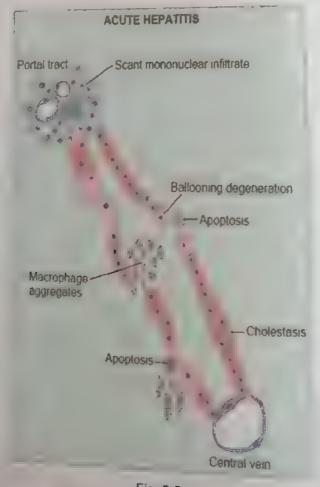


Fig. 9.5

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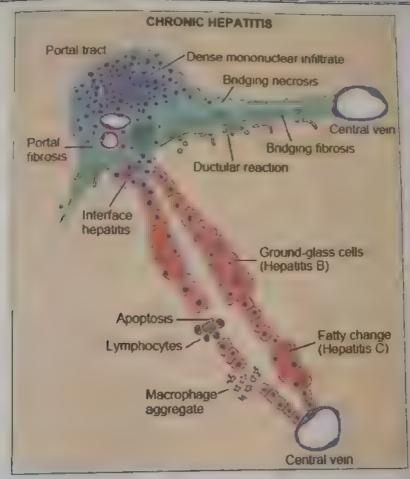


Fig. 9.6

### Acute hepatitis:

DL 85 .

- Ballooning degeneration (Swelling).
- Cholestasis.
- Cel death- Cytolysis apoptosis- councilman bodies.

### Bridging necrosis:

- Hepatocyte swelling and regeneration, loss of radial array.
- Kupffer cell hyperplasia and hypertrophy.
- Portal tracts inflammatory infiltrate.
- · Interface hepatitis, spillage of inflammatory cells from portal tracts into adjacent parenchyma with necrosis

### Chronic hepatitis: Mild to severe.

- Continued interface hepatitis and bridging necrosis.
- Bridging fibrosis.
- Periportal fibrosis, Portal fibrosis

Eventually cirrhosis (post necrotic cirrhosis).



# **HCV** infection: Special features:

- Bile duct damage.
- Steatosis- Macro vesicular type.
- Portal lymphoid aggregates.

### Quick Summary:

- The vowels (hepatitis A and E) never cause chronic hepatitis, only acute hepatitis. except HEV in immunocompromised hosts and pregnant females.
- Only the consonants (hepatitis B, C, D) have the potential to cause chronic disease (c for consonant and for chronic).
- Hepatitis B can be transmitted by blood, birthing, and "bonking" (as they say in the United Kingdom).
- Hepatitis C is the single virus that is more often chronic than not (almost never) detected acutely; 80% or more of patients develop chronic hepatitis, 20% of whom will develop cirrhosis).
- · Hepatitis D, the delta agent, is a defective virus, requiring hepatitis B co-infection for its own capacity to infect and replicate.
- Hepatitis E is endemic in equatorial regions and frequently epidemic.
- The inflammatory cells in both acute and chronic viral hepatitis are mainly T cells; it is the pattern of injury that is different between the two time courses, not the nature
- Biopsy assessment in chronic viral hepatitis is most important for grading and staging of disease, which are used to decide whether a patient undergoes often arduous antiviral treatments.
- Patients with long-standing HBV or HCV related cirrhosis are at increased risk for the development of hepatocellular carcinoma.

### **Fulminant Hepatitis:**

- Progression from onset to hepatic encephalopathy/death.
  - Within 2-3 weeks fulminant hepatitis
  - Within 3 months sub fulminant failure
  - Cause of 50-65% cases of hepatic failure.

### Causes:

- Viral infections: HAV, HBV, HCV, HDV, HEV.
- $\bullet$  Drugs and chemicals: Acetaminophens, INH,  $\alpha$  methyl DOPA, Amantia phalloides.
- Ischemic hepatitis necrosis.
- Obstruction of hepatic vein.
- Massive malignant infiltration of liver.
- Wilson' disease, stroke, fatty liver pregnancy.

Morphology: Liver Shrunk - 500-700 gm's red, limp organ covered by wrinkled Capsule Necrotic areas: Muddy red, mushy appearance. Collapsed Reticulum.

Prognosis: 25-90% mortality in absence of liver transplant.



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# Most common causes in Hepatitis:

- . Acute viral hepatitis in children: Hep A.
- . Acute viral hepatitis in adults: Hep E.
- . Acute viral hepatitis (prevalence): Hep B.
- . Acute viral hepatitis leading to fulminant hepatitis: Hep D.
- , Fulminant hepatitis: Hep E.
- . Epidemic: Hep C.
- , Viral cause of cirrhosis: Hep C.
- . Chronic hepatitis: Hep B.
- , Acute viral hepatitis leading to chronic hepatitis: Hep C.
- . Carrier state: Hep B.
- , Acute viral hepatitis leading to carrier state: Hep B.
- . Viral cause of HCC: Hep B.

### **Autoimmune Hepatitis:**

Histologically similar to chronic hepatitis.

	Points	
Autoantibodies	ANA or ASMA or LKM > 1:80 ANA or ASMA or LKM > 1.40 SLA LP Positive (>20 units)	2
		0
IgG (or garnma globulins)	>1 10 times normal limit Upper normal limit	2
Liver	Typical tor autoimmune hepatitis	2
histology I	Compatible with autoimmune hepatitis Atypical for autoimmune	1
		0
Absence of	Yes	2
viral hepatitis	No	0

### Features:

- Female predominance (78%).
- Absence of viral serologic markers.
- Elevated serum IgG and gamma globulin levels (>1.5 times).
- H gh serum titer of auto antibodies (in 80%of cases) antinuclear, anti-smooth muscle, and /or antiliver/ kidney microsomes antibodies (anti LKMI).
- Negative antimitochondrial antibodies.
- Untreated severe disease leads to death in 40% patients and cirrhosis develops in at least 40% of survivors.
- Rx- Immuno suppressive therapy, liver transplantation.
- Frequency of HLAB of HLA DRW3.

• Other Auto immune disease present 60% patients like R.A, thyroiditis, sjogrens, UC

- Type I- Most common has ANA and / or SMA serum marker. • Type II- Younger patients, anti-liver/ kidney micro some antibodies.

- There are two primary types of autoimmune hepatitis:
- There are two primary types of the seen in middle-aged women and is most.
   Type 1 autoimmune hepatitis is most often seen in middle-aged women and is most. Type 1 autoimmune hepaticis is most often and anti-smooth muscle antibodies characteristically associated with antinuclear and anti-smooth muscle antibodies • Type 2 auto mmune hepatitis is most often seen in children or teenagers and s
- associated with anti-liver kidney microsomal autoantibodies (anti-LKM1).
- Autoimmune hepatitis may either develop with a rapidly progressive acute disease or follow a more indolent path; if untreated, both are likely to lead to liver failure.
- Plasma cells are a prominent and characteristic component of the inflammatory nfiltrate in biopsy specimens showing autoimmune hepatitis.

### Drug Injury:

- Direct injury.
- Conversion of xenobiotic to an active toxin.
- Through immune mechanism.

### Drug- or Toxin-Induced Liver Injury:

- most drugs or toxins affecting the liver may be classified as:
- Predictable hepatotoxins, acting in a dose-dependent manner and occurring in most ndividuals.
- · Unpredictable or idiosyncratic hepatotoxins, which happen in rare individuals and which are often independent of dose.
- Hepatotoxins may cause harm from direct cell toxicity, through hepatic convers on of a xenobiotic to an active toxin, or by immune mechanisms, such as by the drug or a metabolite acting as a hapten to convert a cellular protein into an immunogen.
- The most common hepatotoxin causing acute liver failure is acetaminophen.
- The most common hepatotoxin causing chronic liver disease is alcohol.

## **Drug Reactions**

→ Predictable / Intrinsic

E.g. tetracycline, Acetaminophen, anti-neoplastic agents, CCI<sub>4</sub> Amanita

Unpredictable / Idiosyncratic e.g. Chlorpromazine, sulfonamides, methyldopa, allopuri nol.

0		HEPATOBILIARY SYSTEM   229
A STATE OF THE PARTY OF THE PAR	The second secon	District Constitution of the Constitution of t
Cholestasts	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids, antibiotics HAAFT
Cholestatic	Cholestasis with lobular necro inflammatory activity: may show bile duct destruction	Antibiotics, phenothiazine, statins
Hepatocellular necrosis	Spotty hepatocyte necrosis Massive necrosis Chronic hepatitis	Methyldopa, phenytoin Acetaminophen, halothane Isoniazid
Fatty liver disease	Large and small droplet fat "Micro vesicular steatosis" (diffuse small droplet fat) Steatohepatitis with Mallory-Denk bodies	Ethanol, corticosteroids, methotrexate, total parenteral nutrition Valproate, tetracycline, aspirin (Reye syndrome), HAART Ethanol, amiodarone
Tibrosis and	Periportal and pericellular fibrosis	Alcohol, methotrexate, enalapril, vitamin A and other retinoids
Granulomas	Noncaseating epithelioid granulomas Fibrin ring granulomas	Sulfonamides, amiodarone, isoniazid Allopurmol
ascular lesions	Sinusoidal obstruction syndrome (veno- occlusive disease): obliteration of central vens Budd Chiari syndrome Peliosis hepatis: blood- filled cavities, not lined by endothelial cells	High-dose chemotherapy, bush teas Oral contraceptives Anabolic steroids, tamoxifen
ieoplasms	Hepatocellular adenoma	Oral contraceptives, anabolic

steroids Alcohol, thorotrast

Thorotrast, vinyl chionde

### Alcoholic Liver Disease:

- Hepatic Steatosis.
- Alcoholic hepatitis.
- · Cirrhosis.

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Steatosis Micro vesicular -> Macro vesicular

Initially Centrilobular.

Liver: Enlarged, yellow, greasy. Easily fractured.

Hepatocellular carcinoma

Cholangiocarcinoma

Angiosarcoma

Reversible- till fibrosis appears.

### Hepatitis:

- Hepatocyte swelling and necrosis.
- Mallory bodies: Tangled skeins of cytokeratin intermediate filaments and other protein.
   Also seen in
- a. Alcoholic Liver disease.
- b. Primary Biliary cirrhosis.
- c. Wilson's disease.



- d. Chronic cholestasis syndrome.
  - Neutrophilic reaction.
  - Centrilobular fibrosis and perivenular fibrosis.

### Cirrhosis:

Final and irreversible form

Liver' Initially: Yellow, fatty, enlarged.

Later: Brown, Shrunken non - fatty uniform with micro nodules -> broad expanses of tough, pale, scar tissue.

Pathogenesis: Short term, <80gm: → Mild, reversible fatty change.

>80gm, daily → ↑ risk of severe hepato injury.

>160 gm, 10-20 years → severe injury

10-20% Alcoholics have cirrhosis.

Women More susceptible.

# Cause of alcohol induced liver damage:

- 1. Hepatocellular steatosis Cause
  - Shunting of normal substrates from catabolism to lipid synthesis due to increase NADH by alcohol dehydrogenase and acetaldehyde dehdrogenase.
  - Increased peripheral catabolism of lipid, impaired assembly and secretion of lipoprotein.
- 2. Induction of cytochrome P 450.
- 3. Free radical generation.
- 4. Direct effect on micro tubular and mitochondrial function and membrane fluidity.
- 5. Immunologic attack of hepatic neoantigens.
- 6. Intrahepatic glutathione levels (GSH) sensitizing the liver to oxidative injury.

### Cause of Death:

- Hepatic coma.
- Massive GIT bleeding.
- · Intercurrent infection.
- Hepatorenal infection.
- HCC: 3%-6%.

Non Alcoholic steato hepatitis.

- Obesity most important Risk factor.
- Type II DM.
- Hypertriglyceridemias.

# Metabolic Disease of Liver:

- 1. Hemochromatosis.
- Excessive body Fe.
- Genetic / hereditary AR condition.

Chromosome 6 (HFE gene- regulates intestinal absorption of dietary iron).

. Linked to HLA- A3 halotype.

Cysteine -- Tyrosine at AA282 of HFE gene in H/C.

Secondary.

Parenteral Fe overload.

Ineffective erythropoiesis.

Increased oral Fe (Bantu disease).

Congenital A tranferinemia.

· Chronic liver disease.

Total body Fe pool: 2-6 gm.

Liver: 0.5gm (98% in hepatocytes).

In genetic H/C: Fe > 50 gm (>1/3 in liver)

Male...>Female....5th - 6th decade.

Micro nodular cirrhosis (all patients).

Skin pigmentation.

· DM (75%-80%).

Defect in intestinal Fe absorption . . Fe accumulation of 0.5-1gm / years. Disease manifestation > 20gm.

### Iron Causes:

Lipid peroxidation (by Fe catalyzed free radical reactions).

· Stimulation of collagen formation.

Direct interaction of iron with DNA.

### Morphology:

15

· Deposit on of hemosiderin in Liver, pancreas, myocardium, pituitary, adrenal, thyroid, parathyroid, joints and skin.

Cirrhosis (Micro nodular).

· Pancreatic fibrosis.

L ver Periportal hepatocytes: golden yellow hemosiderin granules Pearls+ ve reaction.

No inflammation.

### Hepatitis Fe content:

(N) :< 1000 μg/gm dry weight of liver</li>

Genetic hemochromatosis :> 10,000 µg/gm weight of liver.

Cirrhosis > 22,000 µg/gm weight of liver.

### Pancreas: Pigmented.

Fibrosis in interstitial tissue.

Parenchymal atrophy.

H'siderin' in acinar and islet cells.

Heart: H 'siderin' in myocardial fibres Heart is enlarged.

Skin: H 'siderin' in dermal macrophages and fibroblasts.

1 epidermal melanin production (results n pigmentation) state gray color Bronze diabetes.

### 232 | PATHOLOGY

# Testes - Small and atrophic.

- · Cirrhosis.
- Cardiac disease.
- HCC risk increase 200 times.

Screening technique for family members of probands.

- · S ferritin & Iron.
- HLA gene molecular analysis.
- Liver biopsy.

### WILSON'S Disease:

Accumulation of toxic level of Cu in liver, brain, eye (Hepatolenticular degeneration).

AR

Ingested Cu absorbed

In stomach / duodenum

(2-5mg)

Plasma Cu with albumin — ► Liver — ► Cu-α₂ globulin

Ceruloplasmin Comes into plasma (90.95% plasma Cu)

Desialylated Ceruloplasmin

Degraded Bile

Total body Cu: 50-150 mg

Gene: ATP 7, chromosome 13

- Encodes transmembrane Cu transporting ATPase.
- Located at hepatocyte canalicular membrane.

Def: Excretion ⇒ Cu accumulation in liver.

Non- Cerulopalsmin bound Cu spills in plasma by 5 years of age.

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Eye: Jsual

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Hemolysis 'Urinary Cu

Pathologic damage to brain Bone, joint, parathyroid, Cornea, kidney

# Morphology: Fatty change.

- . Acute and chronic hepatitis .
- , Mallory bodies Acute stage.
- · Cirrhosis.
- . Massive liver necrosis Rare.

Excess Cu: Rhodanine / Orcein Stain.

Hepatic CU> 250µg/gm dry weight of Liver

5. Cerulopasmin < 20 mg/dl.

J. Cu>30-50 µg/24 hours

Brain: Toxic injury to basal ganglia: Putamen.

Eye: Kayser Fleischer Rings (deposit in Descemet membrane).

Usually manifest after 6 years of age.

Neuropsychiatric / hepatic manifestations.

### Lab diagnosis:

- · "Decrease serum ceruloplasmin.
- Hepatic copper.
- 'Urinary copper.

### 3. $\alpha_i$ - Antitrypsin Deficiency.

(Protease inhibitor).

- α, AT: synthesized by hepatocytes
- Gene on chromosome 14
- Most common genotype Pi MM (90%)

Deficiency Var: Pi S variant -  $\downarrow$  S- $\alpha$ 1 AT.

PiZZ: 10% of (n)

PiMZ → intermediate

Pi null  $\rightarrow$  no  $\alpha_1$  AT

Def. Variants have defect in movement of secretory proteins from ER to Golgi apparatus. Mutant Polypeptide: abnormally folded  $\rightarrow$  hindered movement of  $\alpha$  ATZ peptide 1 retention in E.R.

# Morphology:

Round to oval cytoplasmic inclusion.

Eosinophilic, PAS+ve diastase resistant



Int

### 234 | PATHOLOGY

C/F → Neonatal hepatitis with cholestatic jaundice in 10-20% newborns with the deficiency. Cirrhosis by middle to late life.

HCC: 2-3%

Neonatal Hepatitis / Cholestasis: 1 in 2500 births: Neonatal Repatitis / Ottos are crucial in D/D of neonatal hepatitis and biliary atres a. Neonatal hepatitis - Prolonged, conjugated hyper bilirubinemia.

### Histopathology:

- Lobular disarray with focal liver necrosis.
- Paniobular giant cell formation of hepatocytes.
- Hepatocellular & canalicular cholestasis.
- Mononuclear infiltration (periportal) with kupffer cell hyperplasia).
- Extramedullary hematopoesis.

### Neonatal cholestasis - Causes:

- 1. Extra hepatic biliary Atresia (20%).
- 2. Idiopathic Neonatal hepatitis (50%).
- 3. Neonatal infectious CMV, Bacterial Sepsis, UTI etc.
- 4. Toxic Drugs.
- 5. Metabolic diseases-
- α IAT Deficiency (15%).
- Niemann Pick disease.
- Galactosemia.
- Cysticfibrosis.
- 6. Miscellaneous shock, ICC.

### Quick Revision:

- the most common metabolic disorder is nonalcoholic fatty liver disease, which s associated with the metabolic syndrome, obesity, type 2 diabetes mellitus or other mpairments of insulin responsiveness, dyslipidemia, and hypertension.
- Nonalcoholic fatty liver disease may show all the changes associated with alcoholic liver disease: steatosis, steatohepatitis, and steatofibrosis, even though the features of steatohepatitis (e.g., hepatocyte ballooning, Mallory-Denk bodies, and neutrophilic infiltration) are often less prominent than they are in alcohol-related injury.

### Reye's syndrome:

Encephalopathy following viral infection. H/O Aspirin intake (no role in pathogenesis) Micro vesicular steatosis- characteristic feature (AIIMS question).

# Inherited Metabolic Liver Disease.

- The inherited metabolic diseases include hemochromatosis, Wilson disease, and G1antitrypsin deficiency.
- hereditary hemochromatosis is caused by a mutation in the HFE gene, whose product is involved in intestinal iron uptake by its effect on hepcidin levels. It is characterized by accumulation of iron in liver and pancreas.



- Wilson disease is caused by a mutation in the metal ion transporter ATP7B, which results in accumulation of copper in the liver, brain (particularly basal ganglia), and eyes ("Kayser-Fleisher rings").
- Wilson disease effects on the liver are protean, presenting as acute massive hepatic necrosis, fatty liver disease, or chronic hepatitis and cirrhosis.
- α1-Antitrypsin deficiency is a disease of protein misfolding that results in impaired secretion of α1 Antitrypsin into the serum.
- . The Z variant of  $\alpha 1$ -Antitrypsin is the most likely to impair secretion by hepatocytes and cause disease, particularly when homozygous, that is, the **PiZZ** genotype; the main consequences are pulmonary emphysema caused by increased elastase activity and liver injury caused by the accumulation of abnormal  $\alpha 1$ -Antitrypsin.

# Intra Hepatic Biliary Tr. Disease:

## 1. SEC- BILIARY CIRHOSIS:

Etiology. Extra hepatic bile duct obstruction: stones, atresia, structure, carcinoma. Conjugated bil. ',' S. Alkaline PO<sub>4</sub>ase ' Bile acids 'cholesterol.

C/F Pruritis, jaundice, dark urine, light stools.

M/C bile stasis with bile duct proliferation

) gsaw pattern due to coarse fibrous septae Small and Large bile ducts in septae.

### 2. Primary Biliary CIRRHOSIS:

Female: Male = 6:1 middle age (40-50 yrs).

- · Chronic, progressive, often fatal cholestatic liver disease.
- Destruction of intra hepatic bile dusts- Medium sized ducts.
- Serum Auto antibodies: Anti mitochondrial Ab (in 90%) against E2 subunit of pyruvate. Dehydrogenase complex of (IgM type).
- Extra hepatic manifestation sjogrens syndrome, scleroderma, Thyroiditis, Membranous Glomerulonephritis, celiac disease Reynauds phenomenon.

### Morphology: Focal and variable disease

Diff. Degrees of severity in different portion of liver).

### Stages:

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- Forid duct lesion (by granulomatous inflammation) Destruction of terminal and conducting bile ducts.
- Ductular proliferation.
- Scarring.
- · Cirrhosis.

Bile stained green liver.

Treatment: Liver transplantation.

3. Primary Sclerosing Cholangitis: Inflammation and obliterative fibrosis of intra and extrahepatic bile ducts, with dilatation of preserved segments.

Male: Female ....3-5th decade.

- Obliterative, fibrosing cholangitis (onion skin).
- Segmental obliteration of intra and extra hepatic bile duct.



# 236 | PATHOLOGY

- Beading of Barium column. Associated with IBD (ulcerative colitis in 70%).
- 'risk of cholangiocarcinoma.
- Treatment: Liver transplantation.

# Anomalies of Biliary Tree:

1. Von Meyenberg complex/ Bile duct microhamartomas:

Incomplete involution of embryonic bile duct remnants. Within PT. small clusters of dilated bile ducts embedded in fibrous, stroma

- May communicate with biliary tree.

# 2. Polycystic Liver Disease:

- Multiple diffuse cystic lesions.
- No pigmented material. Detached from biliary tree.

## 3. Cong. Hepatic Disease:

- Pt enlarged by irregular Broad bands of collagen.
- Divide liver into irregular Islands.
- Variable no. of abnormal, shaped bile ducts embedded in fibrous tissue.
  - In continuity with biliary tree.
  - May dev. PHT, 'risk of cholangio Carcinoma.

### 4. Caroli's Disease:

Larger ducts of intra hepatic biliary tree are segmentally dilated and contain inspissated

- C/O: Intra hepatic cholelithiasis, Cholangitis.
- 'Risk of cholangiocarcinoma, Portal H.T.

### 5. Alagille syndrome:

- · Paucity of bile ducts.
- · Un common AD condition.
- Liver (n) but PT bile ducts absent.

Peculiar facies, vertebral abnorm, CVS defects.

Risk of hepatic failure & HCC.

Mutation in gene Jagged 1 on chromosome 20p: encoded ligands for notch 1 (Role in development of organ systems).

# Circulatory Disorders:

- 1. Portal vein obstruction and thrombosis- Extrahepatic / Intrahepatic:
- a. Banti Syndrome: Extrahepatic PB thrombosis.

Subclinical occlusion (neonatal umbilical sepsis/ umbilical vein. Catheterization) presents as ascites and v aricealbleeding years later.

- b. Intraabdominal sepsis:
- c. Thrombogenic disorders (post- surgical):

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Acute intra hepatic PV thromboses produced sharply demarcated area of red-blue discoloration - infarct of zahn.

# Budd- Chiari Syndrome:

- nepatic vein thrombosis Hepatomegaly, weight gain, ascites, abdominal pain.
- Associated with polycythemia vera, pregnancy, post partum state, OCs, PNH intra abd. Ca Idiopathic (30%).

Treatment: Portosystemic shunt,

# Veno-Occlusive Disease:

- Jamaican drinkers of pyrrolizidine alkaloid containing bush tea.
- Now. After BM transplant 25% of patients.
- Obliteration of hepatic vein radicals by endothelial swelling and fine collagen.

Diagnosis by H/O tender hepatomegaly, jaundice ascites; Do not to biopsy as. It can be Catastrophic Pathogenesis? Toxic damage to endothelium.

## Peliosis Hepatitis:

- Sinusoidal dilatation.
- nepatic efflux impeded associated with Anabolic steroids, rarely OCs and danazol.
- HIV infection → Bartonella hensealse infection → Peliosis.

### Heart Failure:

- (R) Heart failure- Passive congestion of liver.
- (L) Heart failure / shock centrilobular necrosis.
- Combination of hypo perfusion and retrograde congestion → centrilobular hemorrhagic necrosis (Nut Meg liver).
- Complication Cardiac sclerosis /cardiac cirrhosis.

# Liver Disease with Pregnancy:

# 1. Pre eclampsia & Eclampsia:

HELLP syndrome.

On liver: Small, red, hemorrhagic patches.

- Periportal necrosis; periportal fibrinoid deposits.
- Hematoma.
- Hepatic Rupture (blood under glissons capsule).
- T/T- Termination of pregnancy.

## 2. Acute fatty liver of pregnancy:

- Latter half of pregnancy (3<sup>rd</sup> trimester).
- Defect in intra mitochondrial FA oxidation.
- Micro vesicular Steatosis with lobular disarray.
- Clinical features of Hepatic failure.

# 3. Intra hepatic cholestasis of pregnancy:

- Mild cholestasis without necrosis.
- 3<sup>rd</sup> trimester.

## 238 . PATROLOGY

1. Most common benign lesions: Cavernous hemangioma - 2cm under capsule.

- 2. Nodular hyperplasia:
- Focal nodular hyperplasia.

Nodular regenerative hyperplasia.

- Affects the whole liver spherical nodules without fibrosis. Plump hepatocytes are surrounded by rims of atrophic hepatocytes.
- Associated with portal hypertension.
- → Focal nodular Hyperplasia:
- Young to middle age adults female preponderance.
- Asymptomatic / abd. Mass / Discomfort
- No malignant potential.

Path. Weil demarcated non- encapsulated, Nodule Lighter in color than liver.

- Central scar with large vessels (arteries).
- Septae show bile duct proliferation.

Types of hepatocellular adenomas.

- 1. HNF1 α inactivated type:
- 90% of these tumors have inactivating mutations which are somatic; 10% are
- Heterozygous germline mutations are responsible for Autosomal dominant MODY 3
- · Most commonly found in women; OCPs are implicated in some.
- · These tumors are devoid of cellular and architectural atypia and are fatty
- · Almost no risk of malignant transformation.
- Liver fatty acid binding protein (LFABP) [downstream regulated protein of HNF1  $\alpha$  s constitutively expressed in all normal hepatocytes but is absent in these tumors.
- IHC for LFABP showing absence is diagnostic.
- β catenin activated type:
- associated with neoplasia and malignancy in many organs
- Very high risk for malignant transformation in liver
- should be resected even when asymptomatic.
- associated with oral contraceptive and anabolic steroid use.
- found in both men and women.
- High degree of cytological and architectural dysplasia.
- ullet IHC for eta catenin shows nuclear translocation indicative of its activated state. Glutamine synthetase (target of beta catenin) is also diffusely positive in these
- 3. Inflammatory type:
- Both men and women.
- associated with NAFLD.
- Small but definite risk of malignant transformation.
- characterized by activating mutations in gp130, a coreceptor for IL-6, that leads to

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Malign: 1. Hepa

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3. HCC

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constitutive JAK-STAT signaling and overexpression of acute phase reactants.

have areas of fibrotic stroma, mononuclear inflammation, ductular reactions, dilated sinusoids, telangiectatic vessels

Most of these tumors overexpress acute phase reactants such as CRP, serum amyloid

Some have  $\beta$  catenin activating mutations too.

SOFT STATE OF THE	Electronic I
Adenoma	Oral contraceptive exposure Glycogen storage disease type la [Von Gierke disease).
Hepatocellular carcinoma	Viral hepatitis, Hepatitis B infection. Hepatitis C infection. Cirrhosis from other causes. Alcoholic liver disease. Hereditary haemochromatosis. Hereditary tyrosinaemia. al -antitrypsin storage disorder. Wilson disease (rare). Primary biliary cirrhosis (rare). Inherited disorders without obligate cirrhosis. Glycogen storage disease type 1a (Von Gierke disease).
Hepatoblastoma	Familial adenomatous polyposis (FAP)
Cholangiocarcinoma	Primary sclerosing cholangitis.  Fluke infection of the biliary tract.
Angiosarcoma	Toxin expo5LreJ Vinyl chloride Arsenic

Historic ty. Thorotrast exposure was a risk Factor for hepatocellular carcinoma, chelangiocarcinoma and angiosarcoma,

### **Malignant Tumors:**

### 1. Hepatoblastoma



-Young children (most common liver tumor of early childhood- rarely occurs >3 yrs)

Epithelial type--- small polygonal cells/ embryonal cells forming acini tubules

Mixed epithelial / mesenchymal type

- Contain primitive mesenchyme
- 2. Angiosarcoma:
- Vinyl chloride, Arsenic, thorotrast
- 3. HCC: 90% of primary carcinoma of Liver:
- HBB and HCV infection.

### Ратногою 240

- Cirrhosis (alcoholic cirrhosis)/ hemo chromatosis.
- Hereditary tyrosinemias , 40% dev. HCC. Universal HBV vaccination may decrease incidence of HCC.
- Unifocal single large mass.
- Multi focal multiple nodules.
- Diffuse Involves entire liver.
- Cells are bile stained.
- Tendency of invade vascular channels.
- Well → poorly differentiated.
- Fibrolamellar Ca: 20-40 years.
- No associated with circhosis / HBV.
- Better prognosis.
- HrP Schirrous tumor- fibrous bands and well differentiated polygonal cell in nests
- ↑ α FP levels.
- 4. Cholangio Carcinoma Ca of extra / intra hepatic biliary tree.
- · Thorotrast.
- Opisthorchis sinensis.
- · Caroli's disease.
- Prim. Cholangitis.
- Cong. Hepatic fibrosis.
- Lymphatic and vascular invasion prominent.
- Extensive intra hepatic metastases.
- LN mets → Perihilar, Peripancreatic, para- aortic LNs.

Hematog. Mets  $\rightarrow$  lung, bones, adrenals, brain.

(Less with HCC than cholangio Ca).

Most common - Adenocarcinomas with marked desmoplasia.

· Not bile stained.

Death: Cachexia.

GIT bleeds/ variceal bleed.

Liver failure.

Rupture of tumor.

Premalignant lesions for cholangiocarcinoma are also known, the most important of which are till ant of which are biliary intraepithelial neoplasias (low to high grade, BilIN-1,

Metastatic tumors: More common in liver than primary tumors (most common neoplasm of the liver).

MC primary: colon > Breast.

Multiple nodular implants with umblilcation.

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# Quick Revision:

- . Hepatocellular adenomas are benign tumors of neoplastic hepatocytes. Most can be subclassified on the basis of molecular changes:
- HNF1- inactivated adenomas, with virtually no risk of malignant transformation, often associated with oral contraceptive pill use or in individuals with MODY-3.
- , -Catenin activated adenoma, with mutations in the  $\beta$ -catenin gene leading to marked atypia and associated with a very high risk for malignant transformation.
- . Inflammatory adenomas, the hallmark of which is up-regulation of C-reactive protein and serum amyloid A (often derived from gp130 mutations); 10% of these have concomitant β-catenin activating mutations. Risk for malignant transformation is intermediate.
- The main primary malignancies are HCCs and cholangiocarcinomas; HCCs are by far the most common.
- HCC is a common tumor in regions of Asia and Africa, and its incidence is increasing in the United States.
- · The main etiologic agents for HCC are chronic hepatitis B and C, alcoholic cirrhosis, non-alcoholic fatty liver disease, and hemochromatosis. In the Western population, about 90% of HCCs develop in cirrhotic livers; in Asia, almost 50% of cases develop in noncirrhotic livers.
- · The chronic inflammation and cellular regeneration associated with viral hepatitis or the activation of IL-6/ JAK STAT pathway may be predisposing factors for the development of carcinomas.
- HCCs may be unifocal or multifocal, tend to invade blood vessels, and recapitulate normal liver architecture to varying degrees.
- Cholangiocarcinoma is endemic in areas where liver flukes such as Opisthorchis and Clonorchis species are endemic. Chronic inflammatory diseases of bile ducts are also risk factors. The tumors may arise from extra hepatic or intrahepatic bile ducts. They have uniformly poor prognosis.



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Concept: Gastrointestinal Tract

Concept: Gastrointestinia, Gastric carcinoma, Malabsorption syndromes (Celiac Learning Objectives: Gastritis, Gastric carcinoma, Malabsorption syndromes (Celiac Learning Objectives: Gastritis, Gastrite Bolyps, inflammatory bowel diseasesColonic Abetalipoproteinemia, Whipples), colonic polyps, inflammatory bowel diseasesColonic carcinoma Focus of tables

## Time Needed

18 vanding	75 hours
1" reading	30 mins
2 <sup>nd</sup> reading	30 11110

Hirschsprung Disease

• Results when the normal migration of neural crest cells from cecum to rectum is arrested prematurely or when the ganglion cells undergo premature death.

 This produces a distal intestinal segment that lacks both the Meissner submucosal and the Averbach myenteric plexus ("aganglionosis"). Coordinated peristaltic contractions are absent and functional obstruction occurs, resulting in dilation proximal to the affected segment.

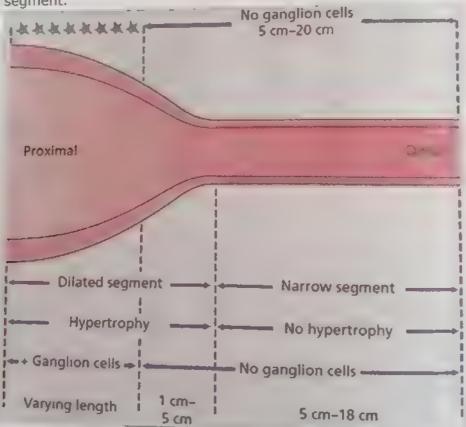


Fig. 10.1: Schematic diagram of gross and microscopic changes in 15 cases of Hirschsprung disease

- Heterozygous loss of- function mutations in the receptor tyrosine kinase RET account for the majority of familial cases.
- Diagnosis of Hirschsprung disease requires documenting the absence of ganglion cells within the affected segment
- In addition to their characteristic morphology in hematoxylin and eosin-stained sections dendling colleges and eosin-stained for the colleges and the colleges are colleges are colleges and the colleges are colleges are colleges are colleges are colleges are colleges and the colleges are colleges sections, ganglion cells can be identified using immunohistochemical stains for acetylcholinesterase.



The rectum is always affected.

Intraoperative frozen-section analysis is commonly used to confirm the presence of ganglion cells at the anastomotic margin

### Barret's Esophagus

Barrett esophagus is a complication of chronic GERD that is characterized by intestinal metaplasia within the esophageal squamous mucosa.

The greatest concern in Barrett esophagus is that it confers an increased risk of esophageal adenocarcinoma.

. Barrett esophagus is most common in white males and typically presents between 40 and 60 years of age

. The presence of dysplasia, a preinvasive change, is associated with prolonged symptoms, longer segment length, increased patient age, and Caucasian race.

Recognized as one or several tongues or patches of red, velvety mucosa extending upward from the gastroesophageal junction. This metaplastic mucosa alternates with residual smooth, pale squamous (esophageal) mucosa and interfaces with lightbrown columnar (gastric) mucosa distally

. Ava able data suggest that the risk of dysplasia correlates with length of esophagus

. Dagnos s of Barrett esophagus requires endoscopic evidence of metaplastic columnar mucosa above the gastroesophageal junction.

· Microscopically, intestinal-type metaplasia is seen as replacement of the squamous esophageal epithelium with goblet cells.

 These are diagnostic of Barrett esophagus, and have distinct mucous vacuoles that stain pale blue by hematoxylin and eosin and impart the shape of a wine goblet to the remaining cytoplasm.

 Special stains like PAS and alcian blue at low pH can be used to demonstrate mucin in goblet cells characteristically.

#### Mechanisms of Gastric Injury

### H. Pylori and Autoimmuno Gastritis

l. Pylori and	Autoimmune Gastritis	
		Autojmmune
Location	Antrum	Body
Inflammatory Infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to decreased	Increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to H. pylori	Antibodies to parietal cells (H+.K++ AfPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, MALToma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autonmmune disease thyroiditis, diabetes mellitus, Graves disease

Occurs in 15% to 20% of patients. Most frequent complication May be life-threatening. Accounts for 25% of ulcer deaths May be the first indication of an ulcer

#### Perforation

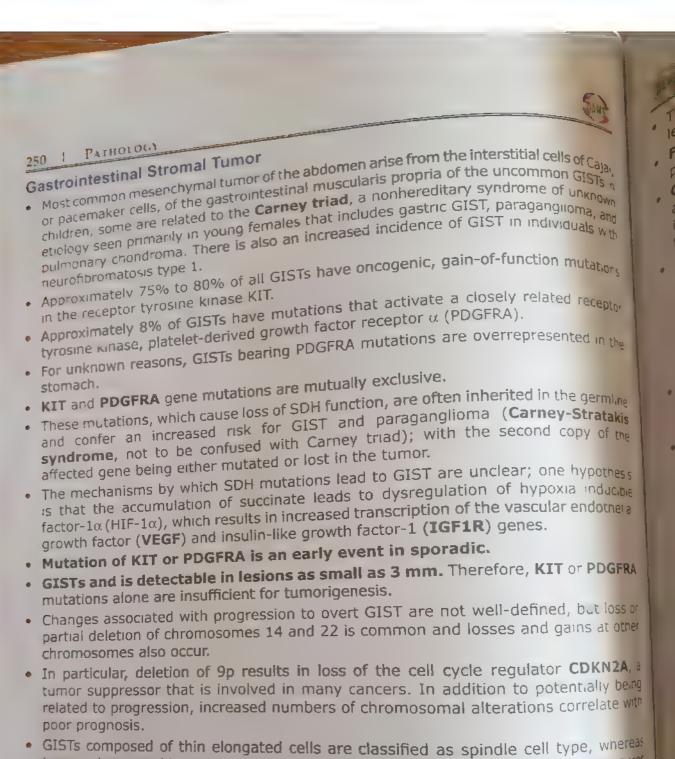
Occurs in up to 5% of patients. Accounts for two thirds of ulcer deaths. Is rarely first indication of an ulcer

#### Obstruction

Mostly in chronic ulcers. Secondary to edema or scarring Occurs in about 2% of patients. Most often associated with pyloric channel ulcers. May occur with duodenal ulcers Causes incapacitating, crampy abdominal pain Can rarely cause total obstruction and intractable vomitin

trophic Gastropathies and Gastric Polyps

	dulti	Syndrome	Hamma and Hype plasue Polyps	eysuc		
Mean patient	30-60	50	50-60	Variable	50	50-60
I - ution	Body and fundus	Fundus	Antrum > body	Body	Body and fundus	Antrum >
Predominant cell type	Mucous	Parietal - mucous, endocrine	Mucous	Mucous. cyst-lining	Parietal and chief	Dysplastic, intestinal
Inflamm a try into date	Limited, lymphocytes	Neutrophils	Neutroph Is and lymphocytes	Neutrophils and lymphocytes	None	Var.able
Symptoms	Hypo proteinemia weight loss, d,arrhea	Peptic ulcers	Similar lo chronic gastritis	Similar to chronic gastritis	None. nausea	Similar to chronic gastritis
Risk lictors	None	Multiple endocrine neoplasia	Chrome gastritis, H. pylori	Iraama, prior surgery	PPIS, FAP	Chrome gastritis, atrophy, intestinal metaplasia
Association with adeno-	Yes	No	Occasional	No	Syndromic (FAP) only	Frequent



tumors dominated by epithelial appearing cells are termed epithelioid type; mixtures

• The most useful diagnostic marker is KIT, which is detectable in Cajal cells and 95%

• Ménétrier disease is a rare disorder caused by excessive secretion of transforming growth factor  $\alpha$  (TGF- $\alpha$ ) and characterized by diffuse foveolar hyperplasia and protein losing enteropathy

Zollinger-Ellison syndrome is caused by gastrin-secreting tumors that cause parieto cell hyperplasia and acid hyper social cell hyperplasia and acid hyper secretion; 60% to 90% of gastrinomas are malignant.

of the two patterns also occur.

 Most sensitive marker- CD 117. Most specific marker- DOG1.

of gastric GISTs by immunohistochemical stains.

Neoplastic and Non neoplastic proliferations of the stomach

- The majority of gastric polyps are inflammatory or hyperplastic polyps, reactive The man are associated with chronic gastritis.
- Fundic gland polyps occur sporadically, most often as a consequence of proton pump inhibitor therapy, and in familial adenomatous polyposis (FAP) patients.
- Gastric adenomas develop in a background of chronic gastritis and are particularly Gastric advisor in pastric adenomas which therefore associated with gastric adenomas, which therefore require more aggressive therapy is frequent in gastric requirement in gastric adenomas, which therefore require more aggressive therapy than adenomas of the colon.
- Gastric adenocarcinoma incidence varies markedly with geography. Individual Gastric according to location, gross, and histologic morphology. Gastric tumors with an intestinal histology tend to form bulky tumors and may be tumors while those composed of signetring cells typically display a diffuse infiltrative growth pattern that may thicken the gastric wall without forming a d screte mass. Gastric adenocarcinomas are linked to H. pylori induced chronic
- . Primary gastric lymphomas are most often derived from mucosa-associated lymphoid tissue (MALT), whose development is induced by chronic gastritis that is most often induced by H. pylori.
- . Carcinoid tumors (well-differentiated neuroendocrine tumors) arise from diffuse components of the endocrine system and are most common in the GI tract, particularly the small intestine. Prognosis is based on location; tumors of the small intestine tend to be most aggressive, while those of the appendix are typically benign.

Defects in Malabsorptive and Diarrheal Diseases

refects in Malabsorptiv	Intraluntinal	Termonal	T	Transport
) sease	Digestion	Digestion	Transport	Hansport
Celiac disease		+	1	
		-	+	
Environmental enteropathy				
Chronic pancreatitis	+			
Cystic fibrosis	+			
Primary bile acid malabsorption	+		+	
Caremoid syndrome	1	-	+	
Autoimmune enteropathy				
Disaccharidase deficiency		+		+
Wh.pple disease			+	
Abetailpoproteinemia			-	
Viral gastroenteritis				
Bacterial gastroenteritis		+		
Paras,tic gastroenteritis		1	4	
Inflammatory bowel disease	*	Todacated	. Other processes are r	not affected.

indicates that the process is abnormal in the disease indicated. Of



### Celiac Disease

252

- Celiac sprue or glutensensitive enteropathy. Celiac sprue or glutensenselve or the containing
   It is an immune-mediated enteropathy in genetically predisposed individuals
- foods, such as wheat, rye, or barley, in genetically predisposed individuals
- Celiac disease is triggered by ingestion of gluten, which is the major storage protein of Celiac disease is triggered by ingestion of gluten, gliadin, contains most wheat and similar grains. The alcohol-soluble fraction of gluten, gliadin, contains most wheat and similar grains. The dicontribution is digested by luminal and brush-border of the disease-producing components. Gluten is digested by luminal and brush-border of the disease-producing components of the disease-producing components and peptide that enzymes into amino acids and peptides, including a 33-amino acid α-gliadin peptide that is resistant to degradation by gastric, pancreatic, and small intestinal protease
- Some gliadin peptides may induce epithelial cells to express IL-15, which in turn triggers activation and proliferation of CD8+ intraepithelial lymphocytes
- These gliadin peptides interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and, in turn, can stimulate CD4+ T cells to produce cytokines that contribute to tissue damage
- Associations between celiac disease and other immune diseases, including type 1 diabetes, thyroiditis, and Sjögren syndrome, IgA nephropathy, as well as neurologic disorders, such as ataxia, autism, depression, epilepsy, Down syndrome, and Turner syndrome
- Biopsy specimens from the second portion of the duodenum or proximal jejunum, which are exposed to the highest concentrations of dietary gluten, are generally diagnostic in celiac disease
- The histopathology is characterized by increased numbers of intraepithelial CD8+1 lymphocytes (intraepithelial lymphocytosis), crypt hyperplasia, and villous atrophy
- This loss of mucosal and brush-border surface area probably accounts for the malabsorption.
- In addition, increased rates of epithelial turnover, reflected in increased crypt mitotc activity, may limit the ability of absorptive enterocytes to fully differentiate and express proteins necessary for terminal digestion and transepithelial transport.
- Other features of fully developed celiac disease include increased numbers of plasma cells, mast cells, and eosinophils, especially within the upper part of the lamina propria
- The most sensitive tests are the measurement of IgA antibodies against tissue transglutaminase. IgA anti-endomysial antibodies can also be present. IgG antitissue transglutaminase antibodies may be detected in patients with IgA deficiency
- The most common celiac disease-associated cancer is enteropathy-associated T-celi lymphoma, an aggressive lymphoma of intraepithelial T lymphocytes.
- Small intestinal adenocarcinoma is also more frequent in individuals with cellactions disease. disease



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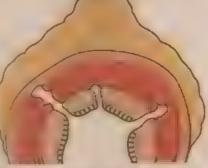
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Inflammatory Bowel Disease CROHN DISEASE **ULCERATIVE COLITIS** 

> Skip lesions

Continuous colonic involvement, beginning in rectum



Ulcer

**Pseudopolyp** 

**Transmural inflammation Ulcerations Fissures** 

Fig. 10.3:

( Features	Licerative Colitis	Cronn biveasi
Clinical		
Rectal bleeding	Common	Inconspicuous
Abdominal mass	Practically never	10-15%
Abdominal pain	Usually left-sided	Usually right-sided
Sigmoidoscopy	Abnormal in 95%	Abnormal in less than 50%
Free perturation	12%	40%
Colon carcinoma	5 10%	Very rare
Anal complications	Rare, minor	75%, fissures, fistulas, ulceration
Response to steroid therapy	75%	25%
Results of surgery	Very good	Fair

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	Rare	Common
Heostomy dysfunction		90%
Radiographic	Excentional	
Sparing of rectum	Rare; dilated ('backwash ileitis')	Common; constricted
involvement of ileum	Absent	Often present
Strictures	Absent	Common
Skip weas	Absent	May be present
Internal fistulas	Exceptional	Common
Longitudinal and transverse ulcers	Absent	Common
Fissuring		Common
Thumb printing	Absent	
Morphologic		Eggal: pradominent.
Distribution of involvement	Diffuse: predominantly left-sided; mucosal and submucosal	Focal; predominantly right saled transmural
Mucosal atrophy and regeneration	Marked	Minimal
Cytoplasnie mucin	Diminished	Preserved
Lymphoid aggregates	Rare	Common
Edema	Minimal	Marked
Нурегениа	May be extreme	Minimal
Granulomas	Absent	Present in 60%
Fissuring	Absent	Present
Crypt abscesses	Common	Rare
Rectal involvement	Practically always	50%
leal involvement	Minimal; dilated not more than 10 cm	50%; constricted; transminflammation
ymph nodes	Reactive hyperplasia	May contain granulomas

### **Intestinal Polyps**

- · Polyps are most common in the colo-rectal region but may occur in the esophagus, stomach, or small intestine.
- Most, if not all, polyps begin as small elevations of the mucosa
- As sessile polyps enlarge, proliferation of cells adjacent to the mass and the effects of traction on the luminal protrusion, may combine to create a stalk.
- Polyps with stalks are termed pedunculated.
- In general, intestinal polyps can be classified as nonneoplastic or neoplastic in nature. • The most common neoplastic polyp is the adenoma, which has the potential to
- The non-neoplastic polyps can be further classified as inflammatory, hamartomatous,



Costrointestinal Polyposis Syndromes

		Syndromes	Gastrointestinal Lesions	Selected Extra- Clastrointestiani Monifestations
<sub>fuvenite</sub> polyposis	< 5	SMAD4 BMPRIA: TGF- S signaling pathway	Juvenile polyps; risk of gastric, small Intestinal, colonic, and pancreatic adenocarcinoma	Congenital malformations, digital clubbing
ال عالم الماري الماري و	10-15	STK11: AMP kinase-related pathways	Arborizing polyps; Small intestine > colon > stomach; colonic adenocarcinoma	Pigmented macules; risk of colon, breast, lung, pancreatic, and thyroid cancer
Cowden Androme. Bannavan- Ravalcaba Riley Androme*	<15	PTEN. PI3K/AKT pathway	Hamartomatous/ inflammatory intestinal polyps, lipomas, ganglioneuromas	Benign skin tumors, benign and malignant thyroid and breast lesions; no Increase In Gl cancers
r mkhilo U mada Wudi mie	>50	Nonhereditary, unkn own cause	Hamartomatous polyps of stomach, small intestine colon; abnormalities in nonpolypoid mucosa	Nail atrophy, hair loss, abnormal skin pigmentation, cachexia, and anemia. Fatal In up to 50%.
Iuberous scierosis		TSC1 (hamartın), TSC2 (tuberin); mTOR pathway	Hamartomatous polyps	Mental retardation epilepsy, facial angiofibroma, cortical (CNS) tubers, renal angiomyolipoma
I annhal adenomatous polyposis FAP Classic FAP Attenuated FAP Gardner syndrome	10-15 40-50 10-15	APC APC APC	Multiple adenomas Multiple adenomas Multiple adenomas	and desmoid tumors, skin cyst
Turcot syndrome MW-associated polyposis	10-15 30-50	APC MYH	Multiple adenomas  Multiple adenomas	Medulloblastoma

adenomatous polyposis.

# Sporadic and Familial Colonic Neoplasias

Sporadic and		Daniel Charles	Transmission		
Etiology	Moiecular Defect	H		The second secon	of horse
Familial adenomatous polyposis (70% of FAP)	APC WNT pathway	APC	Autosomal dominant	None	Tub Jar v has typical acene are sma
Hereditary nonpolyposts colorectal cancer	DNA mismatch repair	MSH2. MLH1	Autosomal dominant	Right side	Sessile service adenominate adel no no including a military
Sporadte colon cancer (80%)	APC/WNT pathway	APC	None	Left side	Tubular, v. 17.5 typical adenocarcin tra
Sporadic colon cancer (10%-	DNA mismatch repati	MSH2, MLH1	None	Right side	Sessile se med adenom in med adenocom nelli.
FAP, Familial		1		1	

### Molecular Carcinogenesis Of Colorectal Cancer

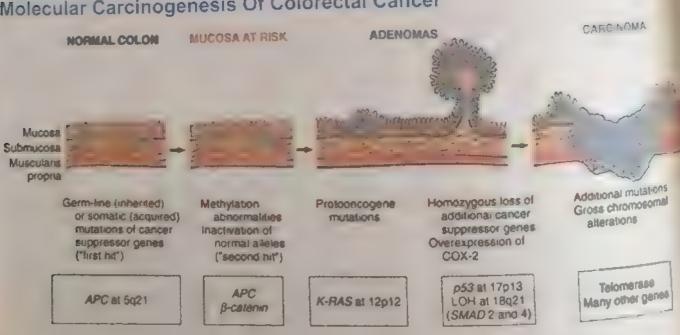


Fig. 10.4:



### **Active Recall**

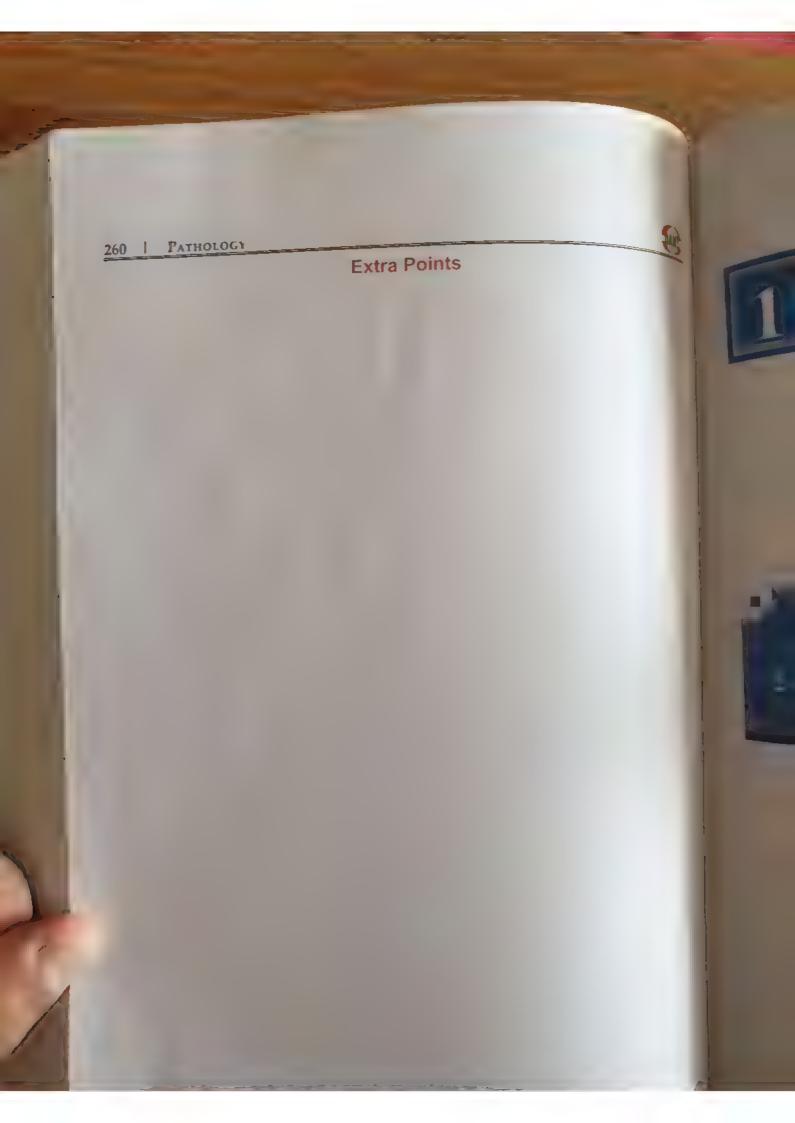
Adenoma caacinoma sequence:

1.

2.

polyps of intestine:

**Ulcerative Colitis and Crohn Disease** 

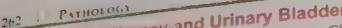




### KIDNEY AND URINARY BLADDER

## CONCEPTS

Cancept U. D. Kidney and Urman Bladder



Concept 11 1: Kigney and Urinary Bladder Concept 11 1. Kidney and Concept 11 1. Kidney Congel

1. Agen

Incor

U/L

Oli

3. EC

4. H

Ell .

		2 hours	
7	1. reading	45 mins	
	2* reading -		

Weight - 150 gm (0.5% of TBW)-25%

Size =  $11 \times 6 \times 3$ cm

Major Calyx (2-3) /Kidney.

Minor calyx-3-4/major calyx, total max-12

90% cortex C.O. ~

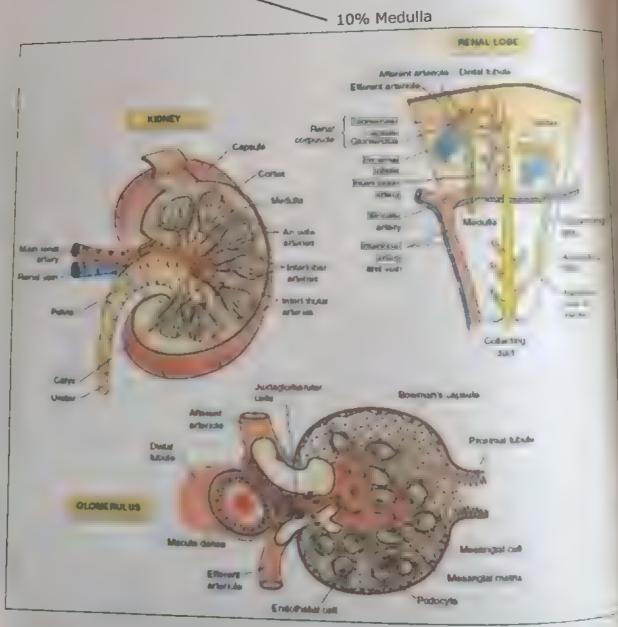


Fig. 11.1



## Congenital Anomalies:

## 1. Agenesis: Total B/L.

Incompatible with life.

Ass. With limb defects, hypoplastic lungs.

U/L

• Uncommon Compensatory hypertrophy (opposite kidney).

### 2. Hypoplasia:

- D/D: Acquired Atrophic kidney.
- · No Scars.

≤ 6 Renal lobes/ Pyramid

Oligomeganepheronia.

Kidney is small but nephrons are hypertrophied.

### 3. Ectopic kidney"

C/o kinking Obstruction. Most common abnormal location-pelvic brim.

#### 4. Horse shoe shaped:

- 1 in 500-1000 pelvic brim.
- Midline anterior to great vessels.
  - 90%: Lower pole.
- 10%: Upper pole.



Fig. 11.2

ystic Diseas	es:			1	
ystic Dioc	The second second	Pathologic			-
Adult polycystic	Autosomal dominate	Large multicystic kidneys, liver cysts, berry aneurysms.	Hematuria, flank pain, urinary tract infection, renal stones, hypertension.	Chronic renal failure beginning at age 40-60 years.	
Childhood polycystic kidney disease	Autosomal recessive	Enlarged, cystic kidneys at birth.	Hepatic fibrosis	Variable, death in infancy of childhood.	
Meduilary sponge kidney	None	Meduliary cysts on excretory urography.	Hematuria, urinary tract infection, recurrent renal stones.	Bening	
Familial juvenile nephronophthisis	Autosomal recessive	Corticomedullary cysts, shrunken kidneys.	Salt wasting, polyuria, growth retardation, anemia.	Progressive renal failure beginning in childhood.	
Adult-onset meduliary cystic disease	Autosomal dominate	Corticomedullary cysts, shrunken kidneys.	Salt wasting, polyuria.	Chronic renal failure beginning in adulthood.	
Multicystic renal dysplasia		Irregular kidneys with cysts to variable size.	Association with order renal anomalies.	Renal failure if bilateral, surgically curable if unilateral.	
Acquired renal cystic disease	None	Cystic degeneration in end-stage kidney disease.	Hemorrhage, erythrocytosis Neoplasis.	Dependence on dialysis.	
S inple cysts	None	Single or multiple cysts in normal- sized kidneys.	Microscopic hematuria.	Bening	3

C 1. 2 3 4



### Classification:

- 1. CRD.
- 2. PCKD.
- 3. Medullary CD.
- 4. Dialysis associated.
- 5. Simple cysts.
- 6. Hereditary malformation syndromes (e.g. tuberous sclerosis).
- 7. Glomerulocystic disease.
- 8 Extraparenchymal renal cysts (pyelo calyceal cysts etc).

### Cystic Renal Dysplasia:

Sporadic with out familial clustering.

- Abnormal Metanephric differentiation.
- · Persistence of abnormal structures (undifferentiated mesenchyme, immature CD, cartilage) & abnormal, lobar organization.
- U/P Obstructions, ureteral agenesis, or atresia.
- Kidney cystic, irregular, enlarged.

#### PCKD:

- Adult (AD) PCKD- potters II.
- Childhood (AR) PCKD- potters I.

#### Child hood PCKD (AR):

Neonatal	common, serious mani festations at birth	
1. Infantile  Juvenile	Assoc. with congenital hepatic fibrosis	

- III Gross: B.L. enlarged kidney. External surface smooth.
  - Cysts oriented in a radial fashion with their long axis at right angles to the capsule.
  - Cysts arise from collecting ducts
- IV. Associations Hepatic cysts, Congenital hepatic fibrosis.
- V. Genes PKHD1 gene 6 p21-23- encodes fibrocystin Role in collecting duct and biliary differentiation.



Fig. 11.3

#### Adult PCKD (AD):

#### 1. Genes-

PKD1- 16p 13.3- Poly cystin I-85%

Found on tubular epithelia cells especially DCT.

Involved in cell - cell and cell - matrix interactions.

PDK2-4Q 21- Polycystin II -10%.

Found in all tubular epithelia cells.

Involved in intracellular Ca2+regulation.

### 2. Chances of developing renal failure-

	PK-U1 Mutations	PND 2 Viorations
By 40 yrs	<5%	
By 50 yrs	~35°,	< 50 o
By 60 yrs	~70%	1500
By 70 yrs	-95%	150
		450

#### 3. C/F:

- Asymptomatic with normal renal function until middle age.
- Presents with renal insufficiency, haematuria and HT.
- Abdominal mass with flank pain.
- Most patients develop end- stage renal failure by their seventh decade.

Mas CYS

5. MICTOS 6 Extra 1

LIV Cyst

. 1/9

. MI , co



### 4. Gross:

- , Massive bilateral kidney enlargement, bulging cysts.
- , Cysts filled with serous, turbid or haemorrhagic fluid.

# 5. Microscopy: Functioning nephrons are present between the cysts:

# 6. Extra renal manifestations:

- Liver cysts (40%) (most common extrarenal manifestation) (\*). Cysts in spieen, pancreas, lung.
- I/C berry anenrysm.
- Mitral vaive prolapse (20-25%).
- · Colonic diverticulae.



Fig. 11.4

#### Meduliary Cystic Disease:

- 1. Medullary sponge kidney.
- Multiple cysts in medulla.
- Arise from collecting ducts Pathogenesis NK.
- C/O: Hematuria, UTI, Calcification stones. 2. Nephonophthisis - Uremic Medullary cystic disease complex-

#### 4. Variants:

- a. Sporadic Non familial (20%).
- b. Familial Juvenile Nephronothisis (40%-50%) AR.
- c. Renal Retinal dysplasia (AR with Retinitis pigmentosa) (15%).
- d. Adult onset Medullary Cystic disease (AD) (15%).



### Clinical Features:

Polyuria, defect in concentrating Ability

Tubular Acidosis.

Salt wasting.

RF in 5-10 years.

Cysts in medulla with cortical tubular atrophy & interstitial fibrosis.

Gross: Small, Contracted with cysts in Medulia, Corticomedullary junction; some cortex.



Fig. 11.5

### 3. Dialysis Associated Cysts:

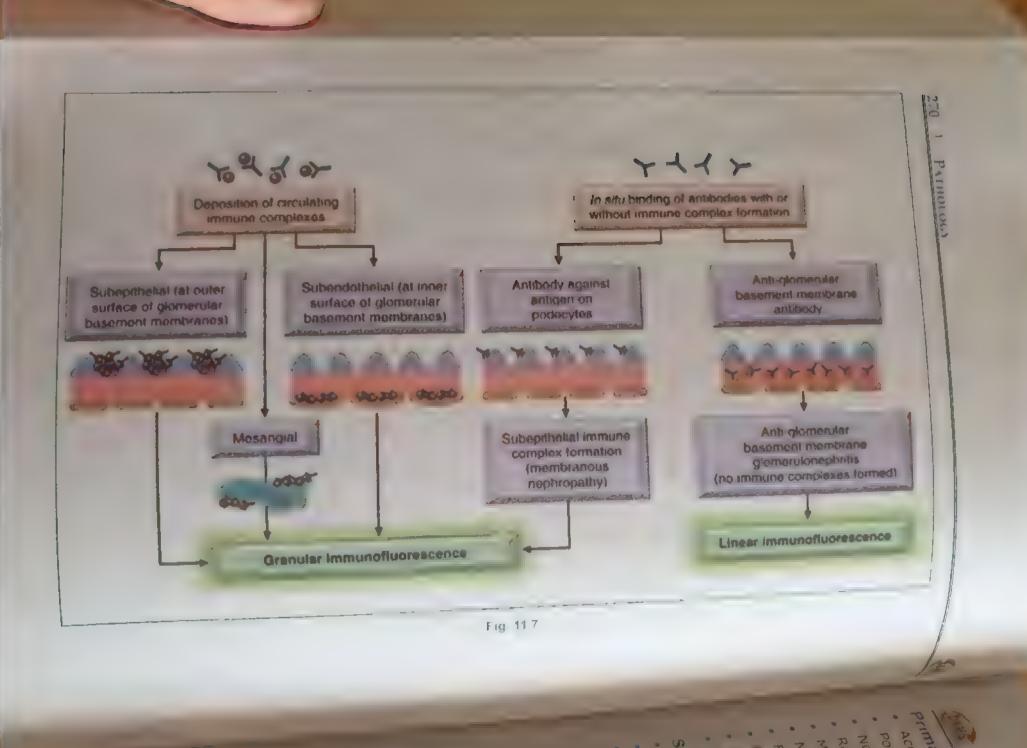
- Prolonged Dialysis.
- Numerous cortical & Medullary cysts
- 0.5 2cm, clear fluid.
- Obstruction by oxalate crystal and interstitial fibrosis.
- Clinically: Asymptomatic, haematuria in some cases.

### 4. Simple Cyst:

- Single or X: in normal sized kidney cortical cyst.
- 1.5 cm, translucent, lined by gray, glistening smooth membrane, Clear fluid Clinically. Asymptomatic; hemorrhage, pain, calcification D/D - Renal tumors.

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# Primary glomerulopathies:

- . Acute diffuse proliferative Glomerulonephritis.
- , Poststreptococcal.
- . Non- poststreptococcal.
- Rapidiy progressive (crescentic) glomerulonephrtitis.
- . Membranous giomerulopathy.
- , Minimal change disease.
- , Focal segmental glomerulosclerosis.
- . Membranoproliferative Glomerulonephritis.
- . Iga nephropathy.
- Chronic Glomerulonephritis.

# Systemic Diseases with Glomerular Involvement:

- Systemic lupus erythematsus.
- · Diabetes mellitus.
- · Amyloidosis.
- Goodpasture syndrome.
- Microscopic polyarteritis / polyangiitis.
- Wegener granulomatosis.
- · Hench- schonlein purpura.
- Bacterial endocarditis.

### Hereditary Disorders:

- · Alport syndrome.
- Thin basement membrane disease.

Fabry disease.	-		the state of the state of the	different Landson
	Cunically	Light Microscopy (H And E, Silver/ Pas Special State)	immuno-	
Minimal change	Nephrotic	No change	Negative	Effacement of foot processes
disease		Focal and segmental	Usually negative	I flacement of foot processes, epithelial
Focal segmental glomerulosclerosis	Predominantly nephrotic	hyalinosis and		denudation.
		Capillary thickening.	Granular 1gG and	Subepithehal deposits
Membranous giomerulopathy.	Nephrotic	"spike and dome"	(3	исрозиз
c more opaniy.		appearance.	Granular IgG, C3,	Subendothelial
Membranoprolifer- dave glomeralone- phras type i	Nephrotic Nephritic	Mesangial and endocapillary proliferation, "tram track" appearance.	Ciq. C4	deposits.

Acute infectious glomerulonephritis	Nephritic	Endocapillary proliferation, mesangial proliferation, leucocytic infiltration.	Granular IgG, C3	Primarily subepithelial (early, subendothelial)
Ig 4 nephropaths	Recurrent hematulia	Mesangial proliteration	IgA + - IgG. IgM, (3 in the mesangium.	Mesangial and paramesangia deposits
Pauci immune glomerulonephritis ( \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	Rapidly proliferative glomerulonephritis	Extra capillary proliferation, crescent formation.	Fibrin in crescents.	No deposits, tragmented GBM

### Nephritic Syndrome:

### Acute Glomerulonephritis-

Inflammatory alterations in glomeruli with nephritic syndrome.

Clin: Acute nephritis. Secondary - SLE, PAN.

Primary

1. Acuteproliferative. Post Streptococcal

Non- Streptococcal Meningococcus, Staphylococcus, pneumococcus Virus: HBV, HCV, HIV, Varicella, IM Malaria, Toxoplasmosis

2. Crescentic GN.

### 1. Acute Proliferative (P. Streptococcal) GN:

Age: 6-10 Years

1-4 weeks after streptococcal infection.

Group A, β hemolytic streptococci.

(Type 12, 4, 1).

Antigen: Endostreptosin, Cationic antigens (proteinase), Nephritis strain associated protein (NSAP).

B/ Chem. ↑ ASO, ↓ serum complement esp C3.

Cryoglobulins (+)

H/P:

Glomeruli: Enlarged, hyprcellular (endothelial cells, mesangial cells, leucocytes)

E/M: Subepithelial, discrete electron dense humps (antigen – antibody complexes)

I/F: Granular deposits of IgG, IgM and C3 throughout the glomerulus.

Clin: Hematuria (Smoky urine/ Cocoa Coloured): Proteinuria (<3g/d).

HT, Qedema, Azotemia.

Spontaneou,

\_\_ Children: 95% Recovery < (5% RPGN, CGN)

Adults: 60% (40% RPGN, CGN)

Complication- Chronic glomeruli nephritis.



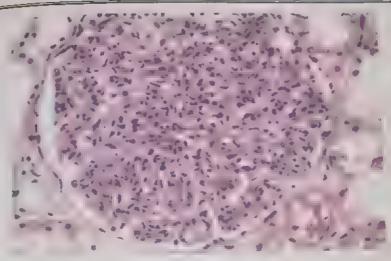


Fig. 11.8



Fig. 11.9



Fig. 11.10



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2. RPGN (Crescentic).

Rapid loss of renal function and severe oliguria with renal failure within weeks to months if not treated.

Crescents formed in Bowman capsule.

### Classification:

Type 1 RPGN / Anti GBM disease:

- Smooth and Linear deposits of IgG, C3 in GBM.
- Antigen resides in alpha 3 portion of Type IV collagen/diopathic.

### Good Pasture Syndrome:

(Pulmonary hemorrhages with renal failure).

Anti GBM anti bodies cross react with pulmonary alveolar basement membrane. M>F, 20-40 yrs.

Pulmonary involvement preceded renal disease.

#### Type II RPGN:

#### (Immune Complex Disease):

Idiopathic -granular pattern of deposits.

Post infectious.

SLE, H-S Purpura etc.

#### Type III RPGN:

Pauci immune / ANCA associated.

Idiopatic IF shows no deposis.

Wegner's granulomatosis (C-ANCA against proseinase 3 in azuroplilic granules). Microscopic Polyarteritis nodosa (P-ANCA against MPO).

Gross: Kidney enlarged, pale with petechial hemorrhage (flea bitten kidney).

### Histopathology:

- Crescents due to proliferation of epithelial cells.
- Infiltration by monocytes & macrophages
- Fibrin strands in between cellular layer in crescent.

### Electron Microscopy:

- Variable, may or may not have electron dense deposits.
- Rupture in BM indicating severe glomerular injury.

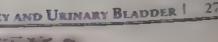




Fig. 11.11

### Nephrotic Syndrome:

Most common cause:

Lipoid nephrosis Children -

Focal and segmental glomerulosclerosis. Adults -

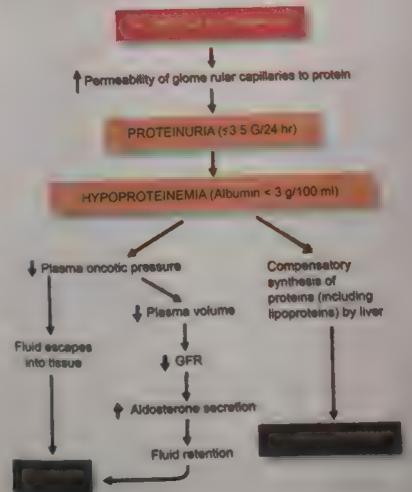


Fig. 11.12: Causes of Nephrotic Syndrome



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### Primary Glomerular Disease: 1. Membranous glomerulopathy.

- 2. Minima change disease. 3. Focal segmental glomerulosclerosis.
- 4. Membranoproliferative GN. 5. Other prolifertive glomerulopathies.

### Systemic Diseases:

Diabetes mell tus.

Drugs (nonsteroidal anti-inflammatory, penicillamine, "street heroin"

Infections (malaria, syphilis, hepatitis B and C

Acquired immunodeficiency syndrome)

Malignant disease (carcinoma, lymphoma)

Miscellaneous (bee-sting allergy, hereditary nephritis) Children less than 15 years → Nephrotic syndrome due to primary kidney cause

	Min.mal-Change Glomerulopathy	Focal Segmental Glome- rulosclerosis	Membranous Glome-rulopathy	Membrano- proliferative Glomerulone- phritis
Light microscopy	No lesion	Focal and segmental glomerular consolidation	Diffuse global capillary wall thickening	Capillary ml thickening and endocapillary hypercellularity
immuno fluorescence microscopy	No immune deposits	No immune deposits	Diffuse capillary wall immunoglobulin	Diffuse capillary wall complemen
m - s- p	No immune deposits	No immune deposits	Diffuse subepithelial dense deposits	Subendothalial (type 1) dease deposits, intra membranous (ty II) dense deposi

## 3. Membranous Glomerulonephritis:

- Characterized by diffuse thickening of glomerular capillary wall & electron dense subeptithelial denosit in RM subeptithelial deposit in BM
- MC cause of nephritic syndrome in elderly

Primary Idiopathic - 85%

Secondary - Drugs, SLE, Infection: (HBV, HCV, syphilis DM, malignancy carcinoma (long, colon). carcinoma (long, colon), melanoma, auto immune diseases

pathog neymal Auto SUD

Bas

Spi

thic Light , Dif

. Ba mm

. GI Elec

Pro



## Pathogenesis:

Auto antibodies against renal glomerular protein megalin (gp 330) neymann nephritis.

Subepithenal deposits of Ig, Complement

Basement membrane material laid down between deposits as spikes

Spikes thicken to produce domes which bury the antibody deposits Membrane thickening encroaches on capillary lumen, sclerosis of mesangium.

### Light microscopy:

- . D ffuse membrane like thickening of capillary walls.
- . Basement membrane projections ("spkes") seen on silver strains.

### Immunoflouroscence;

Granular and linear pattern of IgG and C3.

### Electron microscopy:

- Subep.thelial deposits along the basement membranes.
- Effacement of foot processes of podocytes.

#### Prognosis:

- Variable course.
- 85% Nephrotic syndrome.
- 15% Non Nephritic proleinuria. Poor response to cortico steroids.
- Pers.stent Proteinuria in >60% patients 10% may progress to renal failure within 10 years.

### Minimal Change Disease:

### (Lipoid Nephrosis, Nil Disease):

- Characterized by diffuse loss of foot processes of epithelial cells.
- 2-6 years.
- Selective proteniuria good response to Csteroids.
- Most common cause of NS in children

L/M: (Normal glomeruli, Lipid laden PCT cells).

I/F - Negative; no immune complexes.

E/M NO dense deposits.

Visceral epithelial cells have effacement of foot processes of podocytes.

Retraction, Vasculization & microvillous transformation also seen.

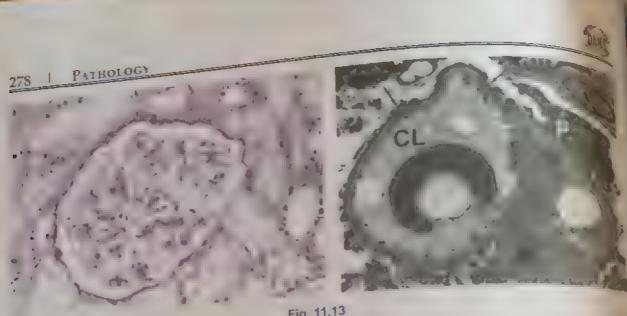


Fig. 11.13

• Associated with respiratory tract infection; immunization; atopic diseases; Mutation in renal glomerular proteins 'Nephrin' (in hereditary: 'Finnish type').

#### Sec:

- Hodgkin's disease.
- Leukemia / lymphoma.
- NSAID therapy.

### Focal Segemental Golmerulosclerosis:

#### a. Clinical features:

- i. African Americans> Caucasians.
- ii. Occurs in all ages.
- iii. Nephrotic syndrome / heavy proteinuria.

#### b. Etiology:

- i. Idiopathic (primary) 10-15% cases.
- ii. Associated with loss of renal tissue U/L kidney agenesis.
- iii. Superimposed on other gomerular diseases, such as IgA nephropathy.
- iv. Sickle cell anemia.
- v. Heroin abuse.
- vi. AIDS.
- vii. Morbid obesity.

viii. Inherited due to mutations ingenes encoding nephrin, podocin,  $\alpha$ - actinin,

#### c. Light microscopy:

- i. Focal segmental sclerosis and hyalinization of glomeruli.
- ii. Initially affects the glomeruli along the medullary border.

Focal: only some of the glomeruli are affected.

Segmental: only a portion of the glomerular tuft shows sclerosis.

d. Immunoflurescence: IgM and C3 deposits in the sclerotic glomeruli are affected segments. segments.

Nonscl Sclero

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e. Electron microscopy: i. Nonsclerotic regions exhibit effacement of foot processes.

i. Sclerotic segments show increased mesangial matrix.

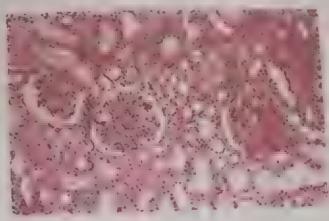


Fig. 11.14



Fig. 11.15

#### f. Treatment:

- i. Poor response to steroids, non selective proteinuria
- ii. High rate of recurrence in renal transplants
- iii. 50% go to end stage renal disease

#### g. Prognosis

- i. Poor; children do better than adults
- ii. Most progress to chronic renal failure

### h. Pathogeneses – Diffuse epithelial damage

Variants: collapsing variant, glomerular tip lesion, peri hilar variant, cellular variant fsgs.

### Collapsing Variant:

Seen in HIV patients.

Rapid down hill course.

Collapse and sclerosis of entire tuft.

Cystic dilatation of tubules.

Tubuloreticular inclusions in endothelial cell.

Membrano Proliferative Gn/Mesangiocapiillary Gn:

10-20% of nephritic syndrome in children / adults.

Double - contour, Tram track appearance.

- Characterized by:
  - alteration in BM.
  - proliferation of glomerular cells.
  - Leukocyte infiltration.

-- Idiopathic Sec. Causes

- 1. Chronic immune complex disorder SLE, HBV, HCV, Endocarditis, HIV, schis to somiasis.
- 2.  $\alpha$  1AT deficiency.
- 3. Malignant diseases (CLL, lymphoma).
- 4. Hereditary complement deficiency.

#### Primary:

Type I: Subendothelial: C3 & IgG.

Activation of classic & Alt. C pathway.

Type II: Lamina densa - irregular ribbon like.

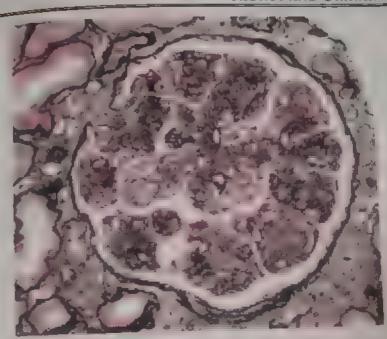
- Dense deposit disease.
- IgG- Absent.
- Activation of alternate C pathway C<sub>3</sub> present but C<sub>4</sub>, C<sub>10</sub> absent.
- IgG- Absent.
- J Factor B & Properdins.
  - C3NeF → stabilizes C3 convertase: also seen in partial lipodystrophy.

#### L/M:

enlarged cellular glomeruli, (mesangial cell proliferation) thickened basement membrane, double contour or tram track due of mesangial, endothelial or leukocyte interposition. PAS/ Silver stain- Double contour or Tram Track.

#### Clin:

Nephritic syndrome haematuria, Proteinuria, RPGN.



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Fig. 11.16

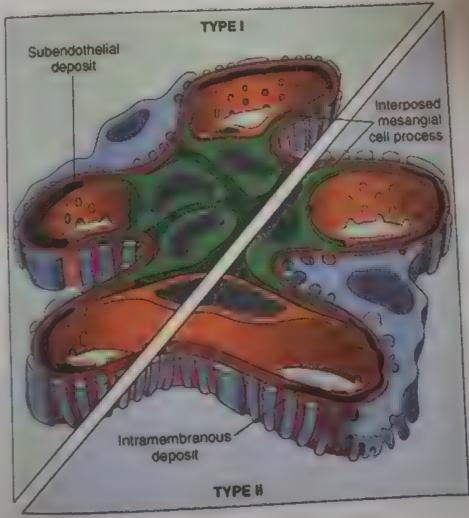


Fig. 11.17



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# IgA Nephropathy (Berger's Disease):

- Most common Glomerulonephritis world wide. • IgA in mesangium, activation of alternative C pathway.
- Gross/Microscopic, haematuria, mild proteinuria.

## IgA deposition seen in:

- Berger's (IgA nephropathy).
- N.S. Farparo.
   Secondary IgA nephropathy (Liver & Int. disease e.g. gluten enteropathy).

IgA Monomeric (n).



c (n). - **Polymeric:** 1 in Berger's disease- alternate complement pathway act. vation

Ag. Unknown

Qualitative alterations in IgA.

L/M: (N) / Mesangial widening & Proliferation or focal proliferation or crescentic. GN I/F: Mesagial deposistion of IgA, C3.

25-50% progress of CRF.



Fig. 11.18

### Focal Proliferative & Necrotizing GN:

Associated with systemic disease: SLE, PAN, SABE, Wegner's

IgA nephropathy.

Idiopathic.

### **Hereditary Nephritis:**

### Alport's Syndrome:

Nephritis and Nerve deafness.

X linked disease with females being carriers, there is increased incidence of a port in females explained by liyon hypothesis (inactivation of X chromosome). Eye Lens dislocation, post, cataract, corneal dystrophy.

E M. GBM Irregular foci of thickening & thinning with splitting & lamination of L densa.

E M. GBM and α3, α4, α5 collagen.

THC Absent to perfect in gene encoding α5 chain of collagen Type IV- defective GBM synthesis in X perfect in gene encoding α5 chain of collagen Type IV- defective GBM synthesis in X

nked disease.

Mulations of α3, α4 chains of type IV collagen in Autosomal recessive (15%)

Mulations microscopic haematuria C nica iy: Gross microscopic haematuria

RBC casts, proteinuria.

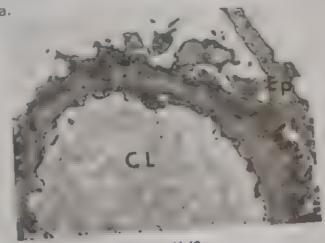


Fig. 11.19

# Thin Membrane Disease (Benign Familial Hematuria):

GBM th nned to 150-225 nm (normal 300-400 nm).

- Hematuria / Proteinuria / Asymptomatic
- . Abnormality in gene encoding  $\alpha 3$  &  $\alpha 4$  chains.

Def: End stage disease characterized by progressive renal failure, uremia and ultimately

death. MGN (50%)

> Slow progression MPGN (50%)

IgA (30-50%

Focal sclerosis Fast progression

RPGN (90%).

Port streptococcal GN (1-2%)

Gross: - Symmetrically contracted Diffusely granular.

M/S hyalinization of glomeruli, interstitial fibrosis, atrophy, of tubules and lymphocytic infiltrate.

Unine Analysis- broad waxy casts.

RX - Dialysis and renal transplantation.

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End stage kidney disease - 30% of IDDM Diabetes affects Glomeruli, arteries & interstitium.

Glomeruli: GBM thickening (2-5 years).

• Offuse Glomerulosclerosis (10-12 years). Office Glomerulosclerosis (10-12 years)
 Office Glomerulosclerosis/ Intercapillary
 Kimmel Steil Wilson disease Nodular Glomerulosclerosis/ Intercapillary

Giomeruiosclerosis

Ovord, laminated hyaline mass-

Periphery of glomerulus.

Within Mesangium.

• Fibrin Cap: Eosinophilic crescents subendothelial (in peripheral capillaries).

- Arteriosclerosis.
- Athermoa of Renal Artery.
- Necrotizing papillitis.
- Pyelonephritis.

## Hencoh - Schonlein Purpura:

Children 3-8 years following URI, atopy.

- Purpuric skin lesions (extensor- Arms, legs, buttocks).
- Abdominal pain, vomiting. Intestinal bleed.
- Non migatory Arthralgia.
- Renal.
- Gross / microscopic haematuria.
- Proteinuria, Nephrotic syndrome.
- RPGN with Crescents.

(C3+IgA+) in Mesangium.

M/S Focal/ Diffuse mesangial proliferation with crescents.

### Amyloidosis:

First in mesangial matrix.

B/M thickening.

## **Tubules & Interstitium:**

1. Acute tubular necrosis (ATN):

- a. Definition: acute renal failure associated with reversible injury to the tubular
- b. Clinical features.
- i. ATN is the most common cause of acute renal failure in the United States.
- ii. Oliguria and elevation of blood urea nitrogen (BUN) and creatinine. iii. Metabolic acidosis and Hyperkalemia.
- iv. Unnalysis shows dirty brown granular casts and epithelial casts.



### not Acute Tubular Meurusia and Acute Pubular Injury

schemic Prerenal Acute Renal Failure or Ischemic Acute Tubular Injury

Massive hemorrhage

Septic shock

severe burns

Dentalration

Posterd diarrhea

conjective heart failure

Wight ed stribution (e.g. pancreatitis, peritonitis)

Nephrotoxin Acute Tubular Injury

aminoglycosides, amphotericin B)

R Journphile contrast agents

How metals (e.g., mercury, lead, cisplatin)

(15 and solvents (e.g., ethylene glycol, carbon tetrachloride)

Fishers : paraquat)

Iseme Protein Cast Nephropathies

Magazine, from rhabdomy olysis, e. g., with crush injury)

Hemoglobin (from hemolysis, e.g., with transfusion reaction)

#### Types:

- C. Ischemic ATN:
- i. Is the most common cause of ATN.
- ii. Is due to decreased blood flow caused by severe hemorrhage,
- lii. Vasoconstriction, hypotension, dehydration, or shock.
- d Nephrotoxic ATN, Caused by:
- i. Drugs (e.g. polymyxin, methicillin, gentamicin. Sulfonamides).
- ii. Radiographic contrast agents.
- ili. Heavy metals (e.g. mercury, Acidophilic inclusions), lead, gold).
- iv. Organic solvents (e.g. carbon tetrachloride, fatty change, chloroform, methyl alcohol).
- V. Ethylene glycol (antifreeze) ballooning and vacuolar degeneration.
- vi. Mushroom poisoning.
- vii.Phenol.
- viii, Pesticides.
- ix. Myoglobin.
- Most vulnerable PCT:

286   PATHOLOGY	sis in Acute Renal Failure
	Urinalysis Sediment Findings
Causes of Acute Renal Failure	Dirty brown casts and epithelial cells
Acute tubular injury	Red blood cell casts and proteinuria
Acute glomerulonephritis	White blood cell casts and pyuria
Acute rubalomterstitual nephritis	

Gros

## Pyelonephritis (PN):

Tubules, Intestitium & Renal Pelvis.

- Acute PN- associated with UTI.
- Acute PN- associated with others (Vesicouretire reflux, obstruction etc.)
   Chronic PN- infection associated with others (Vesicouretire reflux, obstruction etc.)

   Protous Klebsiella- mostly from associated with others. 85%: gram negative bacilli: E. coli, Proteus, Klebsiella- mostly from patients on faecal flora.
  - Small urethra.
  - Absence of antibacterial properties in vaginal fluid.
  - Hormonal changes.

#### Acute PN:

- Patchy interstitial neutrophilic infiltration.
- Tubular necrosis Glomerular sparing.

### Complications:

- 1. Papillary necrosis bilateral, pyramids, distal 2/3rd have grey white necrosis. Other causes.
- DM.
- · U tract obstruction.
- Analgesic Abuse Nephropathy.
- Sickle ceil anemia Renal TB.
- 2. Pyonephrosis complete obstruction.
- 3. Perinephric Abscess- pyelonephritic scar.

### Associated with:

- U tract obstruction.
- Instrumentation.
- Vesicoureteric reflux.
- Pregnancy 4-6% present as bacteruria 20-40% have UTI.

Presence of Leucocyte casts indicate renal involvements.

Chronic PN: inflammation & renal scarring associated with pathological involvement of the calvees & polytic the calyces & pelvis.

10-20% of CRF is caused by Chronic PN

Chronic obstruction

**Most** Important



prugo de hypersensitivity nephritis eg. Sulfonamide penicillin, NSAID – fever, cosino 1. Acute hypersensitivity nephritis eg. Sulfonamide penicillin, NSAID – fever, cosino Drugs & Toxins: plulia rash, renal abnormality.

## 2. ATH.

3. Chronic renal in sniff. Gross - kidneys irregularly scarred:

Coarse, discrete, C/M scar, overlying blunted, dilated & deformed calyx

. More in upper & lower poles.

M/S - Thyroidization of tubules.

- Degeneration and regeneration of epithelial lining.
- Interstital fibrosis and chronic inflammation infiltrate.
- · Periglomerular fibrosis.
- xantnogranulomatous PN: Macrophages (foamy) with plasma cells & giant cells.
- Associated with Proteus infection & obstruction.

## Analgesic Abuse Nephropathy:

- A pap ae are at same stage of necrosis important for D/D of diabetes.
- Pap ary necrosis followed by tubulointerstitial nephritis.
- Phenacet n Acetaminophen; covalent binding and oxidative damage.
- CO Transitional Papillary Carcinoma of renal pelvis.

	C. C	cinoma di Tellai per	Sickle Cell Anaemia	Obstruction
Male: Female	13	1.5	11	91
Be coulse	10Y	7Y	1	V 90%
ריו	8() <sup>6</sup> 0	25%	Dara	Frequent
timedecil	Rare	Freq.	Rare Lew	V
number of Papil a	Several	Almost all All at same	different Stages of necrosis	
	Stages	3(250, 01 11661,010		

#### NSAIDS:

- · Ac Renal failure.
- Membranous GN.
- Lipoid Nephrosis.
- Acute HS interstitial nephritis.

## **Urate Nephropathy:**

- Ac. Uric acid nephropathy-Precipitation of crystals in tubules, CD⇒ obstruction & ARF Precipitation favoured in acidic urine.
- Chronic Urate Nephropathy Ppt. of crystals in DT. CD & interstitium (Birefringent, need e like crystals surrounded by, foreign body giant cell & fibrosis → Tophus) Cortical atrophy & scarring.
- Nephrolithiasis 22% in gout.

Benign Nephroscleorsis:
Sclerosis of Renal arterioles & small blood vessels – focal ischemia of parenchyma.

 HT, DM, ↑ age. Grossly (N) to ↑ size.

Grain leather appearance.

- Hyaline arteriosclerosis & ↓ lumen
- Fibro-elastic Hyperplasia (interloubular and arcuate arteries). Reduplication of elastic LaminaMyofbroblastic tissue in intima.

# Malignant HT / Accelerated Nephrosclerosis:

L/M: fibrinoid necrosis, Necrotizing arteriloitis intravascular thromobosis.

- Hyperplastic Arteriloitis / onion skinning (interlobular arteries) (Concentrically) arranged smooth muscle cells & collagen).
- Necrotizing Glomerulitis Increase level of Renin.

## **Renal Artery Stenosis:**

2-5% of HT, curable.

Most comm. Cause.

- www.Atheroma of Renal Artery
- Fibromuscular dysplasia -3 type intimal, medial, adventitial. (Medial most common).
  - Young females (30-40yrs).
  - · Kidney small with atrophic tubule, crowded glomeruli, interstitial fibrosis.

## **Thrombotic Microangiopathies:**

- Thrombosis in capillaries & arterioles.
- Microangiopathic hemolytic anemia.
- Thrombocytopenia.
- Renal failure.

## Classification:

- 1. Classic childhood HUS verocytotoxin producing E. coli (0157: H7)].
  - Sudden onset: GI influenza like, Prodromal episode hematemesis, malena. oliguria, MAHA neurologic changes.
- 2. Adult HUS, associated with.
  - Infections- endotoxin shigella, (shiga) E. coli septicemia, typhoid fever.
  - Antiphospholipid Ab syndrome.
  - C/O of pregnancy of Contraceptives.
  - Vascular renal disease hypertension, scleroderma.
  - · Chemotherapy.

Familia

down 4. Idiopa cleave Gross

Micro pathogi Endothe & activi

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Arteri Chrol DIabi

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Familial HUS- Inherited deficiency of complement regulatory protein factor H (breaks down C3 convertase).

down to down the Idiopatric (Protease vwf). CNS involvement dominant renal involvement in 50% patients. Gross - Kidney shows patchy / wide renal cortical necrosis. Gross -glomruli with thickened capillary wall with fibrin deposits.

## pathogenesis:

Endothelial injury & activation

Vasoconstriction

platelet aggregation .

Diffuse Cortical Necrosis:

• Fo lowing obstretical emergency; Abruptio placenta, Septic, Shock, Surgery.

DID! of Granular Kidney:

Arteriolar nephrosclerosis fine, regular >1 mm.

Chronic GN- coarse, 1-3 mm.

Diabetic GS.

to stage of Amyloidosis.

Shrunken Kidney	Pe Shial Hemorrhage (9 causes)
	Acute GN- Coagulation disorder
(0)	SABE- Leukemia
C. Albert A	Malign. HT- Epidemic hemorrhagic fever
Danetic Lue stages of Amyloid	Pyuria - Typhus
Cystic disease- Nephronophthisis	Recent infract

#### Renal Infarcts:

- Embolisation from LV/LA.
- Pale grey white infarct.
- · Wedge shaped.

#### Tumors:

N = 1 '41'

10

### Benign:

- 1. Renal Papillary Adenoma < 0.5 cms, cortical.
- Origin tubules.
- Gray yellow.
- 3 Angiomyolipoma associated with Tuberous Sclerosis.
- TS: N/cut, Syndrome. Cortical tubers & Subependymal hamartomas.
- Renal Angiomyolipoma.
- Pulmonary & Cardiac Rhabdomyoma.
- Cysts in liver, kidney & pancreas.

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- Cutaneous: Angiofibromas. Shagreen patch (localized leathery Thickening).
- Ash Leaf patch (hypopigmented).
- Sub ungula fibrous.

#### Genes:

TSC 1- chromosome 9q34 - Hamartin.

TSC2- chromosome 16 p 13.3- Tuberin.

## 4. Oncocytoma:

Tan/ Mahogany brown colour and a central scar.

Origin: Intercalated cell of CD.

Cells: eosinophilic granular – (Because of Mitochondria).

## **Malignant Tumors:**

## RCC/ Hypernephroma:

### Adeno carcinoma:

6-7th decade.

Risk factors: Tobacco, cigarette, obesity, HT, Estrogen therapy.

Asbestos, petroleum, Heavy metal.

1 incid. In CRF, acq. Cystic disease.

## **ASSOCIATED Syndrome:**

- 1. VHL Syndrome AD:
- Retinal angiomatosis.
- · RCC.
- Adrenal pheochromocytoma.
- Cerebellar Hemangioblastoma (also in Retina, Brainstem spinal cord).

COL

Clit

Gene: chromosome 3 p 25.3 → Elongin.

RCC: X, B/L.

### 1. Clear cell RCC:

Sporadic clear cell Ca.

Deletion of chromosome 3.

Hered. Clear ceil Ca.

Unbalanced Transl. of 3; 6, 3; 8, 3; 11

## 2. Papillary RCC:

Sporadic Papillary Ca: Not associated 3 p del.

Hered, Papillary Ca:

Trisomy 7 Activtn of MET.

(MET- p-oncogene; Tyrosine kinase receptor for HGF).

3. Chromophobe RCC: Excellent prognosis, Arises from I/C cells of collecting ducts. Gross: Upper Pole.



Distort Renal Outline. Bright Yellow - Variegated.

Invades Renal Vein.

Collecting duct Carcinoma: Hobnail pattern.

Clinically: Pain, lump, Hematuria. paraneoplastic syndrome: Polycythemia, Hypercalamia, Hepatic dysfunction, feminiparaneophiculanization, Cushing, Leukemoid Reaction, Eosinophilia, Amyloidosis.

## Wilm's Tumor:

Most common primary renal tumor in children.

Age: 2-5 years.

## pathogenesis & Genetics:

1. WAGR syndrome: 33% chances of developing Wilm's. (Wilm's Aniridia genital abnormal; MR) WT-1 gene on chr. 11 p13 (Deletn. / FS/ Non. Sense Mutation).

2. Denys Drash Syndrome.

- . Gonadal dysgensis (male pseudohermophrodite).
- Nephtopathy ⇒ Renal failure.
- WT-1: Missense Mutation.
- 3. Beckwith Wiedemann syndrome.
- Enlargement of body organs.
- Hemihypertophy.
- Renal medullar cysts.
- Adrenal cytomegaly.
- WT-2⇒ chromosome 11p 15.5.
- † risk of developing hepatoblastoma, Adrenocortical & Pancreatic tumors.

Premalignant: Nephroblastomatosis (X diffuse foci of immature nephritogenic elements).

Gross: Solitary, large, well circumscribed

Dwarf's the kidney fish flesh, homogenous

M/S: Blastema.

Epith- Abortive tubules & gomeruli.

Mesenchymal - Cartilage, muscle, fibrous myxoid.

Renal Pelvis, Ureters, Bladder, Urethra- Transitional Ephithelium (3-7 layers in bladder).

### **Brunn Nests:**

- Cystic inclusion of transitional epithelium: Cystitis Cystica.
- Cystic inclusion of intestinal metaplastic epithelium: Cystitis Glandularis.

Hemorrhagic cystitis: associated with chemotherapy, radiation, adeno virus.

Supurative Cystitis.

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- Chronic cystitis.
- Follicular cystitis.
- Eosinophilic Cystics
   Interstitial Cystitis / Huner's Ulcer Persistent, painful form of chronic cystitis
- More frequent in women.
- Associated with inflammation and fibrosis of all layers.
- Ulceration and submucosal oedema.

Grossly: Soft, yellow, slightly raised mucosal plaques; 3-4 cm in diameter.

M/S: Large, foamy macrophages, occasional multinucleate giant cells.

Michalis Gutman Bodies: Laminated mineralized concretions.

· E. coli / Proteus.

## **Tumors of Urinary Bladder:**

95%  $\rightarrow$  Epithelial.

## 1. Urothelial (transitional cell) tumors:

- Inverted papilloma.
- Papilloma (Exophytic).
- Urothelial tumour of low malignant potential.
- Urothelial Carcinoma.
- Carcinoma in situ.
- 2. Sq. cell Ca.
- 3. Mixed Ca.
- 4. Adeno Ca.
- 5. Small cell Ca.
- 6. Sarcoma.

## WHO grading of urothelial tumors:

Papilloma – Rare, ≤ 1% bladder tumors, younger pts., stalked with finger like papillae Normal looking transitional epithelium. Recurrence.

TCC Grade I

TCC Grade II

TCC Grade III

## Grade I: Gross: similar to papilloma

- Cytologic and archet. Atypia (but well differentiated).
- 1 Layers (only slight loss of polarity).
- Seldom invasive, 95% to 98% 10 yrs survival rate.

Grade II: Papillary with flat regions.

- ↑ Layers (>10).
- 1 Mitosis.
- 1 Loss of polarity.

(May be associated with invasion, low risk of progression).

Grade III: Papillary flat, or both.

- Larger extensive, most invasive.
- Disarray, Loosening and Fragmentation of superficial layers.

Necro Local Sp LN: Reg Hemato Carcini High -

> see Stagi Nonti

APP

mas

Lam

Ep



Local spread: Bladder wall, prostate, vesicles, ureter, retroperitoneum.

LN: Regional LNS.

Hematogenous: Liver, lung, Bone Marrow.

Carcinoma in Situ: High - grade flat abnormality confined to bladder mucosa.

- Appear as area of mucosal reddening/ granularity / thickening without intraluminal
- Seen in surrounding areas of invasive carcinoma.

Staging: Depth of Invasion.	
The state of the s	Ta
Noninvasive, papillary	Tis
Carcinoma in sita Noninvasive, flat	TI
Lamina Propria invasion	T2
Masculans propria invasion	ТЗа
Microscopic extravesicle invasion	T3b
Cress,y apparent extravesicle invasion	T4
Invades adjacent Structures	The same of the sa

- LN: N 1-3.
- Distant metastasis → M1.

## **Epidemiology and Pathogenesis:**

- M: F= 3:1, 50-80 yrs.
- Cigarette smoking ↑ risk by 3-7 times.
- Arylamines: β naphthyamine.
- Schistosomia haematobium.
- Long term use of Analgesics.
- Heavy long- term exposure to cyclophosphamdies.
- Deletion of 9 p.
- Deletion of 17 p (Tumor supressor gene p16).
- Mutation of P53, Rb.
  - Two pathway mode: deletion of oncogene on
    - º 9p → p53 mut
    - p 53 mutation
- 10 Years Survival

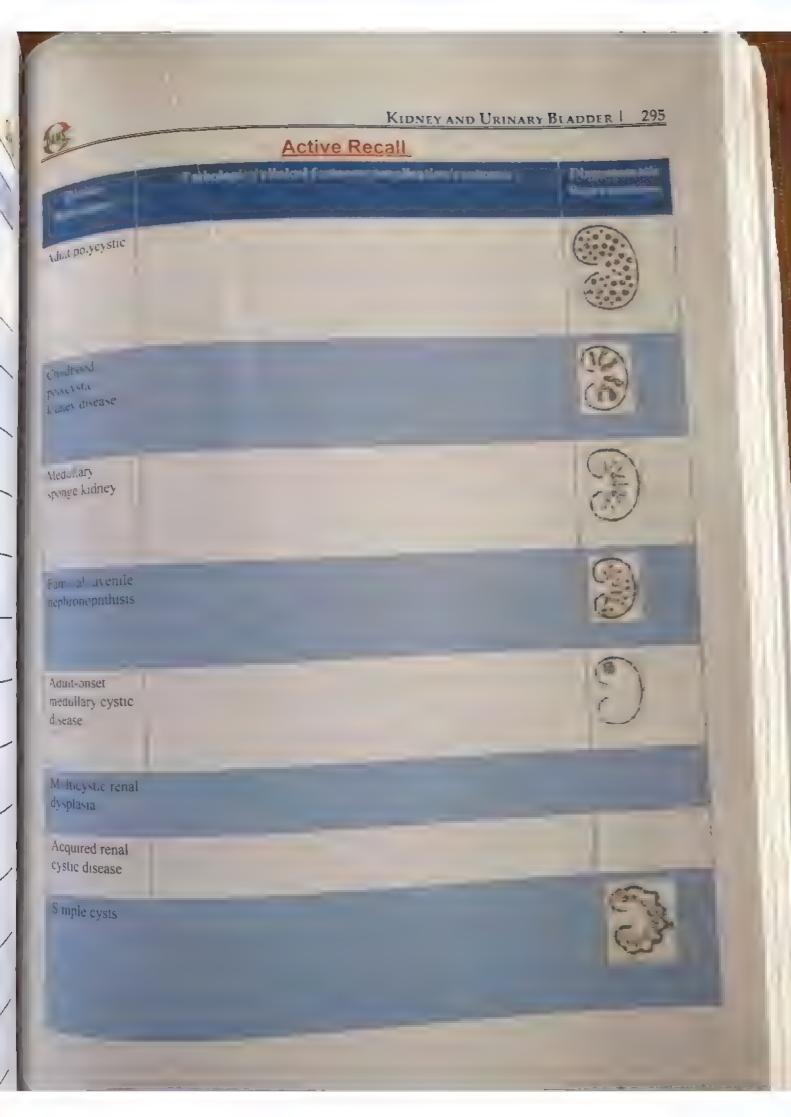
- Recurrence
- Papilloma & Grade I Ca 98%
- Low grade 50%

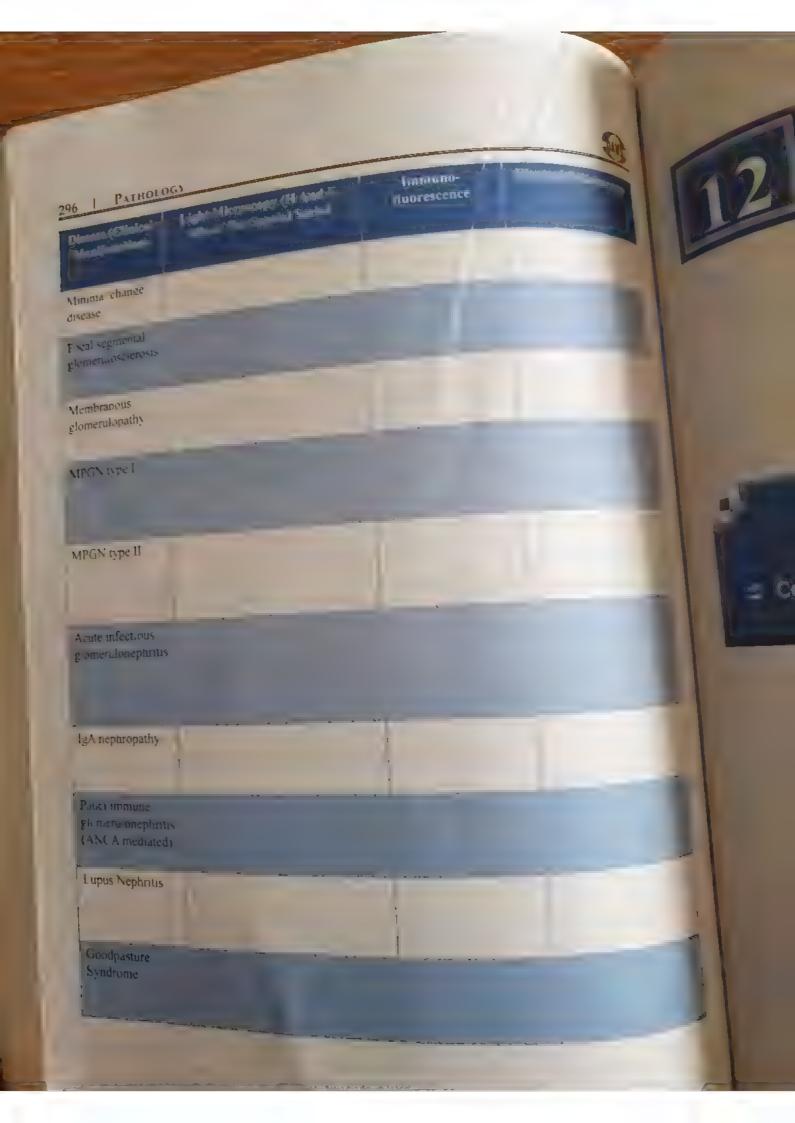
Grade 11 Ca-40%

High grade - 80-90%

Most common benign mesenchymal tumor - Leiomyoma

294 | PATHOLOGY Worksheet Chapter of DQB to be done: • EXTRA POINTS FROM DQB







Concept 12.1: Lung

Learning Objectives: Cystic diseases of Kidney, Glomerulonephritis, renal tumors

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Apnort

featur

75 min I\* reading 30 min 2nd reading

## Respiratory System

## Atelectasis -

Areas of airless lung parenchyma.

- Reversible change.

  Obstructive- Bronchial asthma, COPD, Foreign bodies. Mediastinum moves towards
- Compressive CHF, Air, fluid or blood into the pleural cavity. Mediastinum moves
- away from the affected lung.
- Patchy In Hyaline membrane disease and ARDS.

Commonest source of Pulmonary emboli - Deep veins of leg.

Commonest cause of Pulmonary hypertension- COPD.

Other causes of pulmonary hypertension Recurrent thromboembolic, Endothelial dysfunction. Ingestion of Bush tea, Adulterated olive oil.

Pulmonary infarcts - 3/4th of all infarcts affect the lower lobes. Extend to the periphery of the lung substance with the apex pointing towards the hilus of the lung. Are classically hemorrhagic. Diagnostic feature of pulmonary infarction is the ischemic necrosis of the lung substance within the area of hemorrhage

Scimitar syndrome is a multifaceted malformation characterized by a large anomalous pulmonary vein that drains from one lung, usually the right, into the inferior vena cava. Broad roentgeno- graphic shadow of this Vein forms the scimitar.

Bronchopulmonary dysplasia (BPD) found in infant treated for HMD with O, and artificial ventilation.

Wilson Mihity syndrome - neonatal hyperaeration pulm. Dysmaturity

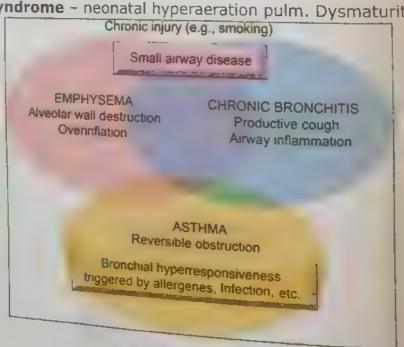


Fig. 12.1:



Emphysema

Employermanent dilatation of acini with destruction of wall without fibrosis. Approximately 50-75 years of age, early dyspnea, Cough is non - productive and a late pack pulled, Cough is non-feature. Infections are rare. Rarely progress to Cor pulmonale. Main pathology is loss of elastic recoil.

#### Types Parine prail Acını enlarged Resp bronchioles Strikingly adjacent to Invariably associated affected, distal from level of resp. pleura along lobular with scarring. Most bronchiole to alveoli spared C.T. septa and at common form terminal blind alveoli margins of lobules Lower zones anterior Upper lobes margin of lungs Cigarette smoking, $\alpha - I$ antitrypsin Adjacent to areas of coal dust def. fibrosis, scarring or (functional) atelectasis Responsible for spontaneous pneumothorax

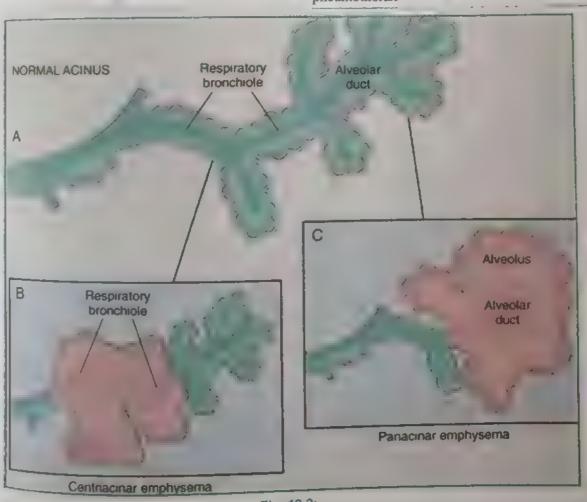


Fig. 12.2:



#### PATHOLOGY 300 |

- Chemotactic for neutrophils + macrophages. Chemotactic for neutrophils + macrophages,
   Release of elastase and other proteases from neutrophils + macrophages, Role of Smoking:
- . Oxidants and free radicals in smoke inhibit  $\alpha$  1 antitrypsin. Oxidants and free radicals in Sition
  Oxidants and free radicals in Sition
  Obstructive over inflation, Bullous emphysema
  Other types - Compensatory, Senile, Obstructive tissue of lung, mediastinum, sub-Other types - Compensatory, Serille, Obstitute tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung, mediastinum, subcutaneous Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitial emphysema - Air in connective tissue of lung in the Interstitute tissues. If extensive it encroaches on blood supply. May be seen in:

Rib fracture

- Chest wound
- Alveolar tears
- Patients with airway obstruction like blood clots, tissue, foreign body Children with whooping cough
- Artificial ventilation

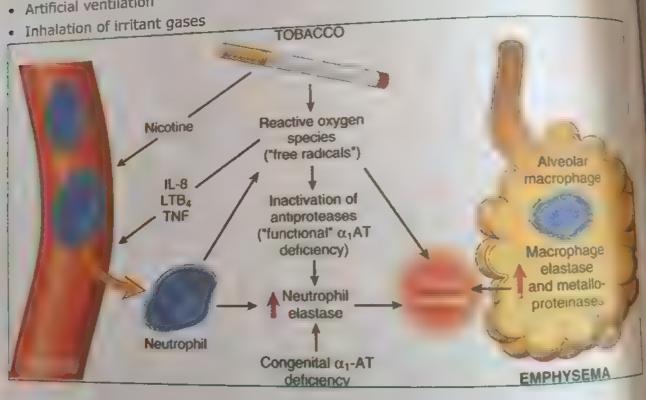


Fig. 12.3:

## **Chronic Bronchitis**

- Persistent cough with sputum for at least 3 months in al least two consecutive years.
- Blue bloaters, Productive cough is an early feature. Cor pulmonale is a more frequent complication.
- Associated with heavy smoking
- Condition is caused by chronic irritation and maintained by recurrent infections. Bronchiolitis refers to inflammation of small airways.

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- Hallmark feature- hypersecretion of mucus associated with hypertrophy of submuscosal glands
- Reid index normal 0.44. In chronic bronchitis means is 0.52. Ratio of the thickness of the mucous gland layer to the thickness of the wall between epithelium and the cartilage links with severity and duration of the disease.
- Other changes include mucous plugs and goblet cell metaplasia in small airways, increased pigment laden macrophages and inflammatory cells, fibrosis, squamous metaplasia and dysplasia of lining of brochi.

## **Emphysema and Chronic Bronchitis**

	Predominant Bronchitis	Predominant Emphysema
Age (yr)	40–45	50-75
Dyspnea	Mild; late	Severe, early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Oceasional
Respiratory insufficiency	Repeated	Terminal
( or pa monare	Common	Rare, terminal
Airway resistance	Increased	Normal or slightly increased
Esac recai.	Normal	Low
Chest radiograph	Prominent vessels; large heart	Hyperinflation; small heart
Appealance	Blue bloater	Pink puffer

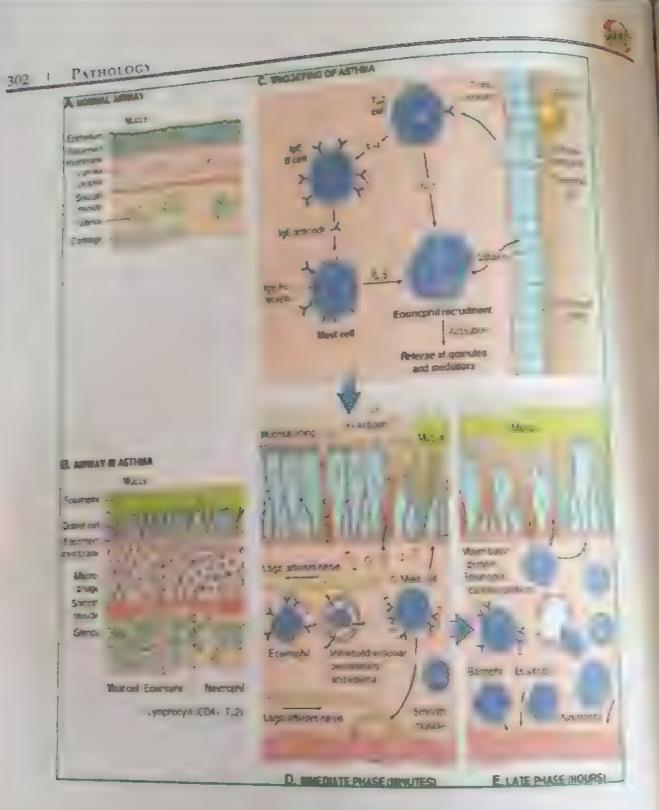
### **Bronchial Asthma**

Hyper responsiveness of tracheobronchial tree to various stimuli potentiating paroxysmal reversible constriction of the bronchial airaways. Usually mediated through type 1

Hypersensitivity

### Types of Asthma

- Atopic (allergic, Extrinsic) → incited by allergen
- Occupational Due to chemical dusts or lume
  - Type 1 IgG mediated
- Allergic bronchopulmonary aspergillosis (Type 1 and 3 reactions)
- Nonreaginic (Intrinsic)
  - Viral respiratory infection (Hyper reactive airway)
- Pharmacologic → Aspirin (Decreased PGs and Increased LTs)



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Fig. 12.3:

Sputum findings- Increased eosinophils, Charcot Leyden crystals and Curschman's spirals.

Histologic features – Bronchial thickening and inflammation with eosinophlilic infiltration, mucous gland hypertrophy

## **Bronchiectasis**

Chronic necrotizing infection of the bronchi and bronchioles associated with abnormal dilatation (permanent) of these airways.



Causes

Bronchial obstruction – Tumors, FB, mucous impaction, Atopic asthma, chronic

b Hereditary - Cystic fibrossi, intralobar sequestration of the lungs, immune-deficiency.

b Hereditary - Cystic fibrossi, intralobar sequestration of the lungs, immune-deficiency. Hereditary syndrome (Immotile cilia, Autosomal recessive. Most common Kartagener's syndrome absent dvenin arms.) abnormality is defective or absent dyenin arms.)

c. Necrotizing pneumonia - TB, Staphylococcal.

Pathology is vicious cycle of obstruction and infection. Patriology affect both lower lobes. Segmental involvement is seen in tumours or FB obstruct on Brochi are dilated upto 4 times normal and can be traced upto the pleural

Types- Cylindroid, fusiform and saccular.

Complication:

Dyspnoea

, Cyanosis, respiratory insufficiency, Cor pulmonale, Metastatic brain abscess, Amyloidosis.

### Pneumonia

Infection of lung parenchyma resulting in consolidation.

Predisposing factors are

- , Impaired host resistance due to chronic diseases, immunodeficiency, Leukopenia
- Highly virulent organisms
- Impaired cough reflex and mucociliary clearance
- Pulmonary congestion and oedema
- Accumulations of secretions
- The Pneumonia Syndromes

## Community Acquired Active Presymonts.

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella catarrhalis

Staphylococcus aureus

Legionella pneumophila

Enterobacteriaceae (Klebsiella pneumoniae) and Pseudomonas spp.

### Community Acquired Atypical Pneumonia

Mycoplasma pneumoniae

Chlamydia spp. (C. pneumoniae, C. psittaci, C. trachomatis)

Coxiella burnetii (Q fever)

Viruses' respiratory syncytial virus, parainfluenza virus (children); influenza A and B (adults), adenovirus multary recruits); SARS virus

## Rospital-Acquired Pneumonia

Gram-negative rods, Enterobacteriaceae (Klebsiella spp., Serratia marcescens, Escherichia coli) and Pseudomonas spp.

Staphylococcus aureus (usually penicillin resistant)

Aspiration raculation (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit Anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admixed with derroit anaerobic oral flora (Bacteroides, Prevotella, Prevotella Anaerobic oral flora (Bacteroides, Prevotella, Pusobacterial, Haemophilus influenzae, and Pseudomonds bacteria (Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and Pseudomonds aeruginosa)

### Chronic Pneumonia

#### Nocardia

Actinomyces

Granulomatous: Mycobacterium tuberculosis and atypical mycobacteria, Histoplasma capsulatum Coccidioides immitis, Blastomyces dermatitidis

## Necrotiving Pneumonia and Lung Abscess

Anaerooic bacteria (extremely common), with or without mixed aerobic infection Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)

## Pneumonia in the Immunocompromised Host

#### Cytomegalovirus

Pneumocystis jiroveci

Mycobacterium avium-intracellulare

Invasive aspergullosis

Invasive candidiasis

"Usual" bacterial, viral, and fungal organisms (listed above)

#### Types are:

- 1. Bronchopneumonia Patchy consolidation. Usually occurs in extremes of age. May be an extension of bronchitis or bronchitis. Causes are mostly Staphylococci, Streptococci.
- 2. Lobar Pneumonia- Consolidation of a lobe or part of a lobe. Common cause 15 Pneumococcus, klebsiella, Staphylococci, Streptococci, H influenzae.

Pseudomonas and Proteus.

## Stages of lobar pneumonia are:

Congestion, Red hepatization (neutrophils + fibrin + extravasation of RBCs); Grey hepatization (fibrin + disintegration of WBCs +RBCs) and Organization or Resolution Complications of Pneumonia are abscess formation, empyemia, Organization and dissemination to distant sites (endocarditis, arthritis, Meningitis).

3. Interstitial pneumonia - Patchy pneumonitis without consolidation. Pleura is smooth and effusions and pleuritis are uncommon. Causes are Viral, Chalmyd.al. Mycoplasma, Rickettsial. (Influenza A and B, RSV, Adenovirus, Rhinovirus, Rubeola and Varicells, Psittacosis and Q fever).

Histologically, alveolar septae are widened with mononuclear infilatration and hyaline membranes, Secondary bronchopneumonia due to secondary bacterial infection may be seen.

Characteristic features in Mycoplasma pneumonia is the presence of cold characteristic features in Mycoplasma pneumonia is the presence of cold agglutinins which are IgM antibodies that do not react at 37°C but cause agglutinations agglutinins which are IgM antibodies and CMV infections.

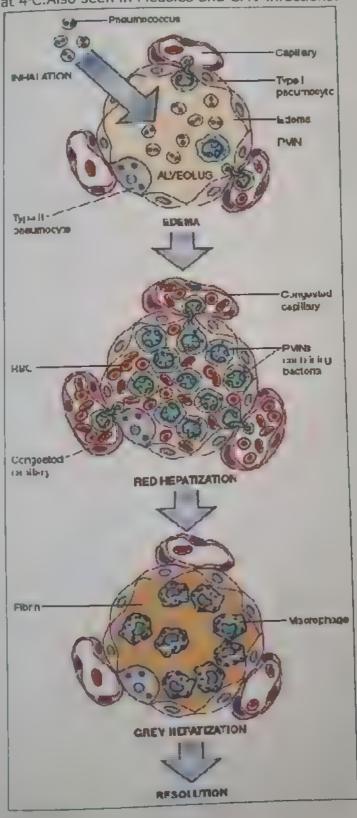


Fig. 12.4:



#### PATHOLOGY 306 |

- Localised suppuration of lung. Associated with. Localised suppuration of lung. Associated material (In comatose, Alcoholic, Most frequent with aspiration of infective material (In comatose, Alcoholic,
- Anaesthetized and debritated patients)
- Oropharyngeal surgery.
- Sino bronchial infections.
- Dental sepsis.
- Bronchiectasis.
- Around pneumonitic patches.
- Septic emboli.
- Neoplastioc obstruction.
- Direct spread or haematogenous spread.

May be few mm to 5-6 cm. Aspiration associated abscess are seen in the right lung

## Chronic Interstitial Lung Diseases:

- D #Use Interstit all fibrosis of the lung gives rise to restrictive lung diseases characterized by reduced ung compliance and reduced forced vital capacity (FVC). The ratio of FEV1 to FVC is normal.
- Id ocathic pulmonary fibrosis is prototypic of restrictive lung diseases. It is characterized by patchy interstitial fibrosis fibroblastic foci and formation of cystic spaces (honeycomb lung). This histologic pattern is known as usual interstitia.
- The cause of idiopathic pulmonary fibrosis is unknown, but genetic analyses point to roles for senescence of alveolar epithelium (due to telomere shortening), cell stress related to protein misfolding, abnormal signaling in alveolar fibroblasts, and altered mucin production. The resulting injury to alveolar epithelial cells set in motion event that lead to increase local production of fibrogenic cytokines such as TGF-B.
- The other diseases that cause diffuse interstitial fibrosis are heterogeneous poorly ur derstood, but most have better prognoses that idiopathic pulmonary fibrosis.

### **Tuberculosis:**

Primary TB- Ghons complex is a primary pulmonary parenchymal subpleural focus Just above or below the interlobar fissure b/w the upper and lower lobes with enlarged caseous yprinode draining it. Usually undergoes fibrosis and calcification. Exceptionally it may progress and cavilate, lead to TB pneumonia or military TB.

Secondary TB following primary TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high Oxygen to the Company TB bacilli establish themselves in lung apices (region of high of h of high Oxygen tension) Secondary TB may be either Reactivation or Reinfection type Secondary lesions are common in the apices as small focus of consolidation. Historogic Hailmark Caseating confluent granulomas with Langhan's giant cells

#### Out come:

- Heal and form a fibrocalcific nodule.
- Progress to.
  - Cavitary Fibrocaseous TB.

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- Advanced Fibrocaseous TB.
- , pleural effusion.
- . Tubercular empyema.
- , Endobronchial/ endotracheal/ intestinal/ Laryngeal TB.
- Miliary TB due to lymphohaematogeneos seeding.
- . End organ TB.
- . TB bronchopneumonia.
- . Lobar exudative consolidation (Galloping consumption).

## Restrictive Airway Diseases:

- , Diffuse chronic infiltrative diseases.
- . Cinically present with dyspnoea, tachypnoea and cyanosis.
- , X ray shows ground glass shadows; diffuse infiltration by small nodules or irregular Ines. Eventually progress to secondary pulmonary hypertension and cor pulmonale.
- . Advanced forms of all entities show gross destruction and fibrosis and appear as Honey comb lung.

	And the state of the Control of the state of
Environmental inhalants	Sarcoidosis
· Inorganic-silicosis, Asbestosis, Berylliosis,	Collagen vascular diseases
Pneumoconiosis	Good pasture's syndrome
· Organic- Hypersensitivity pneumonitis	Idiopathic pulmonary hemosiderosis
· Gases Oxygen toxicity, SO2, Toluene Drugs	Eosinophilic pneumoma
and toxins	Histiocytosis X
Busulphan, Bleomycin, Amiodarone. Gold,	Alveolar proteinosis
Penicillanmine, Paraquat infections	Desquasmative interstitial pneumonia
Viral - influenza, CMV	Usual interstitial pneumonia (Idiopathic pulmonary
• Widespread TB	fibrosis / Cryptogenic fibrosing alveolitis)
• Fungal	
Pneumocustis pneumonia	

In the order of frequency Commonest is Pneumoconiosis followed by sarcoidosis IPF, Collagen vascular diseases.

## Pneumoconiosis:

Non- neoplastic lung reaction to inhalation of mineral dusts. Terms broadened to include diseases caused by organic and inorganic particulates, chemical fumes and vapours.

- Anthracosis is asymptomatic carbon pigmentation of lungs/ draining lymphonodes without any reaction. Seen in coat miners, smokers, urban dwellers. Coal pigment is
- Simple coal worker's pneumoconiosis is characterized by COAL MACULES (1-2 mm) and larger coal nodules which are aggregates of carbon laden macrophages. Common in upper lobes. Can complicate into centrilobular emphysema.



• Complicated CWP is progressive massive fibrosis, which develop rapidly. Complicated CWP is progressive massive modular lesions, which develop rapidly, exposure. Lung show distinct nodular lesions, which develop rapidly.

exposure. Lung show distinct not an independent variable.
 CWP does not pred spose to lung cancer as an independent variable.

- Most prevalent and takes years
   Crystaline forms are Quartz, Crystobalite, Tridymite. More fibrogenic.
- Amorphous forms are Talc, vermiculte and mica. Amorphous forms are Talc, verificance and phospholipids and denatures and damages
   Silica reacts with membrane proteins and phospholipids and denatures and damages
- them. It also incites initialinitiation.

  Nodular fibrosing disease involving upper zone. More fibrosing and less cellular lesions

  Nodular fibrosing disease involving upper zone. Progress to cellular lesions Nodular fibrosing disease trivorving upper
   Nodular fibrosing disease trivorving upper
   Grossly- Tiny discrete pale to blackened nodules in upper zone- Progress to collagenous
- scars. Polarizer reveals silica.
- Superimposed TB cause softening and cavitation.
- Egg sheil calcification in lymphnode.
- No clear cut association with cancer.

### Asbestos:

- Cyrstalline hydrated silicates. Associated with.
- Localized fibrous plaques in pleura (Most common manifestation).
- Pleural effusions.
- Diffuse interstitial fibrosis.
- Bronchogenic CA (5 fold risk).
- Mesothelioma (1000 fold risk).
- Laryngeal and colonic carcinoma.

- 2. Geometric forms Serpentines- Curly and flexible, Eg crysotile. Most common type to exposure. More soluble and easily removed by mucociliary clearance.
- Amphiboles Straight, stiff and brittle. Eg Crocidolite, Amosite, Tremolite.
- Anthophyllite, Actionlyte. Are more pathogenic and lead to mesothelioms. Asbestos bodies or ferruginous bodies are golden brown, fusiform or beaded rods with translucent center of asbestos fibres coated with iron and calcium containing protein. Asbestosis begins with fibrosis around respiratory bronchioles and alveolar ducts. Begins in the **lower lobes** subpleurally.

## Beryllium:

Heavy dose leads to Acute pneumonitis.

Low dose for prolonged duration leads to a pulmonary and systemic granulomatous lesions mimicking sarcoid.

Non caseating graulomas in lung hilar lymphnodes which become progressively fibrotic. Chest X ray shows nodular irregular fine denisities.

### Increased risk of Bronchogenic CA. Others.

Iron - Siderosis Barium sulphate- Baritosis Tin oxide - Stannosis.

Sarcoido Hard n ASSOCI

Uveor Fema diopati

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- Hard non- caseating granulomas in lung with bilateral hilar lymphadenopathy.
- . Associated skin and eye lesions.
- , Uveoparotid involvement (Miculicz syndrome).
- Female predominance.

# Idiopathic Pulmonary Fibrosis:

- . Also called Usual interstitial pneumonitis.
- Chronic interstitial fibrosis. Hamman Rich syndrome. Cryptogenic fibroising alveolitis.
- Characterized by thickened fibrosed inflamed septae with hyaline membranes. Honey comb lung ensues.

Note- Lung fibrosis is a feature of all endstage interstitial diseases like pneumoconiosis, Hypersensitivity pneumonitis, Scleroderma, Collagen vascular diseases, Radiation, Caygen toxicity, Pulmonary hemosiderosis, Drugs like Bleomycin and busulfan. It is not a feature of Leffler's syndrome and Pulmonary alveolar proteinosis.

## Desquamative Interstitial Pneumonitis

Aggregates of macrophages in the alveoli. Ground glass infiltrates in lower lobes. Considered an early stage of UIP. Good response to steroids. Macrophages contain lipid and PASpositive granules

## Hypersensitivity Pneumonitis

A so called extrinsic allergic alveolitis. Immunologically mediated interstitial lung disorder due to inhaled organic dusts.

- Farmer's Lung Due to mouldy hay, Spores of thermophilic actinomycetes
- Pigeon breeder's disease- Due to proteins from serum, droppings and feathers
- Baggasosis- Sugar cane baggasse.
- Humidifier lung Thermophilic bacteria
- Duck fever Feathers
- Mushroom picker's Lung
- Maple bark disease

All are characterized by interstitial pneumonitis, fibrosis, obilterative bronchioliitis and granulomas in lung.

Mediated via type 3 and 4 reactions

## Pulmonary Eosinophilia

Simple or Loeffler's syndrome - Benign

Tropical eosinophilia due to microfilariae in lung

Secondary chronic pulmonary eosinophilia

Idiopathic chronic eosinophilic pneumonia Diagnosis of exclusion after excluding parasites, Fungus, Bacteria, Hypersensitivity pneumonitis, Drug allergy, Asthma, Allergic pronchopulmonary aspergillosis, Churgh strauss syndrome etc.

Respond to steroids



Boop (Bronchiolitis Obliterans Organizing Pneumonia) Boop (Bronchiolitis Obliterans Organizatory Injury to lung. May follow toxic damage, drugs, Response to infection or inflammatory injury to lung. collagen vascular disease, bronchial obstruction.

Rheumatoid Lung
Feature Include Chronic pleuritis, DIP, Fibrosis, Intrapulmonary rheumatoid nodules Caplan's syndrome Pulmonary hypertension.

Palmonary Aiveolar Proteins and PAS positive with lipid. Material significant and precipitate in alveolic PAS positive with lipid. Material significant and precipitate in alveolic page positive with lipid. Material significant and precipitate in alveolic page positive with lipid. Material significant and precipitate in alveolic page positive with lipid. Material significant and precipitate in alveolic page positive with lipid. Material significant and precipitate in alveolic page positive with lipid. Homoceneous quantital precipitate in dispersion and osmiophillic bodies are seen Secreta PAP is associated with Acute Silica exposure, immunocompromised haemato imphoid malignancies, and Opportunistic infections. Accorded PAP accounts for 90% cases. Autoimmune anti GM-CSF antibodies may se pathogenic.

Radiation Damage

Acute radiation Pneumonitis - Shows a picture of DAD Chronic radiation Pneumonitis - Interstitial fibrosis Characteristic feature are epithelial cell atypia with foam cells in vessel wall.

## **Surfactant Dysfunction Disorders**

Sufactant dysfunction disorders are diseases caused by mutations in genes encoding proteins involved in surfactant trafficking or secretion. The mutated genes include the following:

- · ATP-binding cassette protein member 3 (ABCA3) is the most frequently mutated gere in sufactant dysfunction disorders. It is an autosomal recessive disorder and usually presents in the first few months of life with rapidly progressive respiratory facure followed by death. Less commonly it comes to attention in older children and ar adults with chronic interstitial lung disease.
- · Surfactant protein C is the second most commonly mutated gene in sufactant eysfarction disorders. It is autosomal dominant with variable penetrance and seventy 45% and sporadic in 55%. It has a highly variable course.
- Surfactant protein B is the least commonly mutated gene and is associated with an autosorral recessive form of sufactant dysfunction disorder. Typically, the infant is ful term and rapidly develops progressive respiratory distress shortly after birth Death ensues between 3 and 6 months of age.

#### Tumours

Bronchogenic carcinoma is the most common Ca. Predisposing factors are

- Tobacco smoking
- Radiation
- Uranium
- Asbestosis, Berylliosis
- Nickel, Chromates, mustard gas, Arsenic, Iron

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- Gold miners
- Newspaper workers

# Histologic Classification of Malignant Epithelial Lung Tumors

squamous cell carcinoma

Papil ary, clear cell, small cell, basaloid

sma l-cell carcinoma

combined small-cell carcinoma

Adenocarcinoma

Min mally Invasive adenocarcinoma (nonmucinous, mucinous)

epidic, acinar papillary, solid (according to predominant pattern)

Micmous adenocarcinoma

Large-cel carcinoma

Lar e cell neuroendocrine carcinoma

\uenosquamous carcinoma

caremo.nas with pleomorphic, sarcomatoid, or sarcomatous elements

care.no.d tumor

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Tipical, atypical

Carcinomas of salivary gland type

Previous terminology of Bronchioalveolar carcinoma is not used anymore. That pattern is called Adenocarcinoma in situ according to the latest WHO classification.

More than 90% of lung cancers develop as a direct result of exposure to tobacco smoke. Approximately 10% of smokers eventually develop lung cancer.

The gene known to be mutated most frequently in lung cancers is P53. P53 mutations are found in about 50% of NSCLC and in over 90% of SCLC

Many smoking-associated mutations are G →T transversions that occur in known hotspots of the P53 open reading frame.

These characteristic mutations can be directly attributed to bulky adducts caused by exposure to BPDE, a carcinogen in cigarette smoke.

RB is inactivated in 30-40% of NSCLC and in nearly all SCLC tumors.

Among NSCLC, RB mutations are associated with more advanced tumors, implying that RB loss occurs during later stages of tumorigenesis

Scar carcinoma - Mostly adenocarcinoma. Follows old infarcts, Tuberculosis, Metallic foreign bodies and wounds

Commonest type in smokers- Squamous cell carcinoma

Commonest type in women and non smokers- Adenocarcinoma

Ca associated with smoking - SCC, Small Cell Ca

SCC- In and about hilus, Central tumour. Fast growing. Associated with hypercalcemia.

Adeno Ca- Peripheral and slow growing.



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Small cell Ca- Hilar or central, Oat cells growing in clusters, EM shows dense core Small cell Ca- Hilar or central, Oat cells growing the Ectopic hormone production, Most neurosecretory granules. More often associated with Ectopic hormone production, Most neurosecretory granules, the motherapy and radiation. aggressive, Respond to chemotherapy and radiation.

Large cell Ca - Anaplastic, undifferentiated

Other changes with Lung Ch Emphysema, Atelectasis, Bronchitis, Bronchiectasis, Lung Abscess, SVC syndrome.

Percardics ricultions
Concall - Present with cough, weight loss, Chest pain, Dysphoea, Increased sputum, Paraneop astic syndrome associated with lung CA

- · SIADH
- Cushings
- Hypercalcemia
- Hypoglycemia
- Gynaecomastia
- Carcinoid syndrome
- Eaton Lambert Myaesthenic syndrome
- Peripheral neuropathy
- Acanthosis nigricans
- Leukemoid reactions
- --pertrophic pulmonary osteoarthropahty and clubbing

## Bronchioalveolar Carcinoma

now called Adenocarcinomain situ - with Mucinous features)

Per priera les on, May be multiple nodules or pneumonia like consolidation.

30 yrs onwards.

Tall columnar mucin secreting cells in papillary formation May be bronchiolar cells, Clara ce or rarely type II pneumocytes.

Tumor does not involve major bronchi, therefore atelectasis, emphysema are infrequent Metastasis not widely disseminated.

### Neuroendocrine tumours

Tumorlets / Carcinolds / Small cell CA

Carcinoids form 1-5% of lung tumors. Of tumours diagnosed as Bronchial adenoma 96% are carc noids. Others are adenoid cystic and mucoepidermoid carcinoma.

Grossly - 3-4 cm polypoidal lesion projecting into the bronchial lumen or producing a collar button lesion by fanning into peribronchiolar tissue.

Mostly do not have secretory activity and do not metastasize.

Lung hamartoma. Coin lesion on X ray. 3-4 cm. Composed of mature haline cartilage

### Metastasis

Most common Brain Most Specific adrenal



Mesonie or parietal pleura. Very rare without asbestos exposure. Asbestos bodies

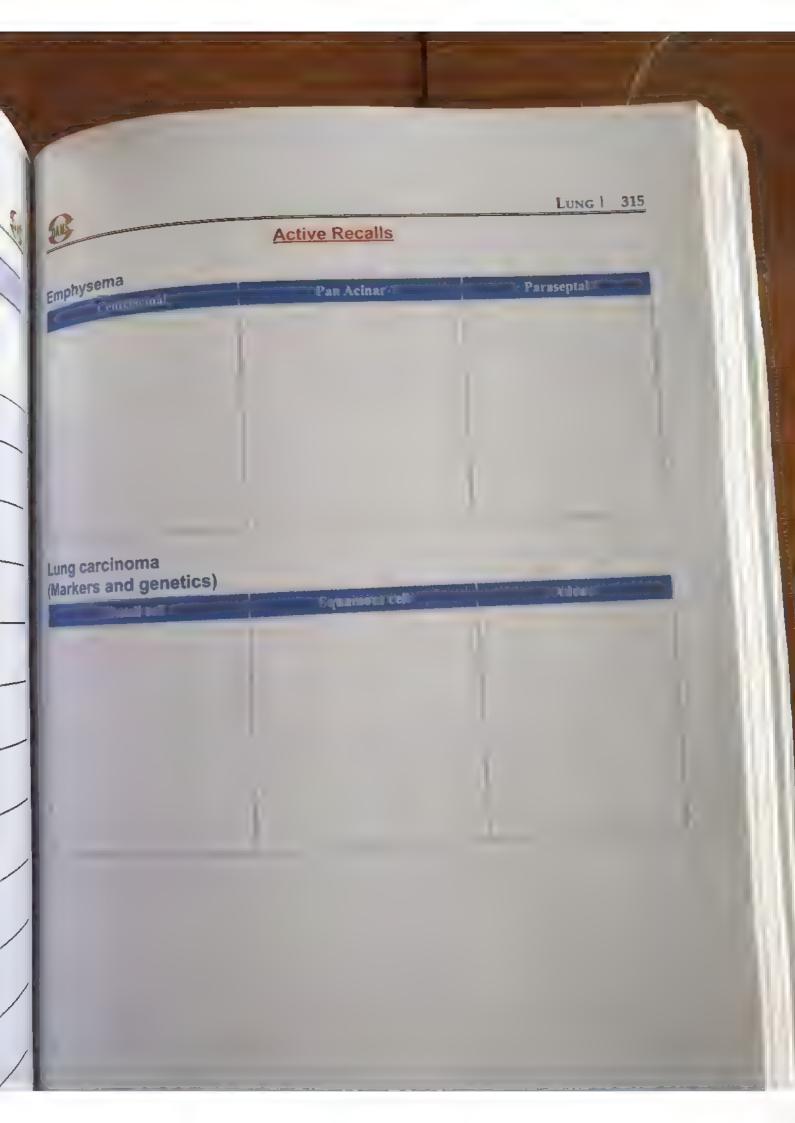
Affects visceral or parietal pleura. Very rare without asbestos exposure. Asbestos bodies Affects viscent. Shows epithelial, sarcomatoid or mixed pattern.

positive for acid mucopolysaccharides which is inhibited by hyaluronidase. Lack of CEA or LeuM1, Positive for Keratin.

EM- Shows long microvilli and abundant tonofilaments. No microvillous rootlets and ame ar bodies seen.

## Lung transplantation

The most common indications are end-stage emphysema, idiopathic pulmonary fibrosis, cystic fibrosis, and diopathic/familial pulmonary arterial hypertension.











# HEMATOLOGY IN NEWBORN AND PREGNANCY

### CONCEPTS

E Lancept 13 I Hematology in Newborn and Pregnancy



Ell

Concept 13 1 Hematology in Newborn and Pregnancy

Learning Objectives. His without, at car on stages of life.

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swireading.

Red Blood Cells:

• Hematoporesis is first established won after implantation of the blastocyst, with the

Hematopoiesis is first established scells in blood islands of the yo'k sur pary none appearance of primitive erythroid cells in blood islands of the yo'k surpary none of primitive erythroid cells in blood islands of the yo'k surpary none of primitive erythroid cells in blood islands of the yo'k surpary none of the you'k surpary none of the yo'k surpary none of the you'k surpa · After 7 weeks gestation, hematopoletic progenitors are no longer detected

• The liver serves as the primary source of red cells from the 9th to the 24th was the

• Ok sac, where nematopoiesis is restricted to maturing primitive - manage, and megakaryocytic cells, hematopolesis in the feta ... renative erythroid, megakaryocyte, and multiple myeloid, as was as d lineages.

· Hematopoietic cells are first seen in the marrow of the 10- to 11-week embry man confined to the diaphyseal regions of long bones until 15 weeks

• PSIS is present in the lymph plexuses and the thymus beginning at 9 weeks gestation.

· \_\_\_\_\_ that mesonephros (AGM) region generates hematopoletic stem cells that . - and the marrow to provide lifelong hematopolesis (\*).

• - \* \* \* \* \* \* \* . , .s the major hemoglobin in embryos younger than 5 weeks. (\*)

Hgb F (α,γ,) is the major hemoglobin of fetal life (\*).

\*\* Got eve in cord blood at term is 16.8 g/DI (\*)

· The red cells of the newborn are macrocytic, with a mean corpuscular volume (MCV , + /CH 1+

decline more rapidly in the following 5 to 8 weeks, producing the co, across of the newborn.

• Segmented neutrophils are the predominant leukocytes in the first few days

As their number decreases, the lymphocyte becomes the most numerous cell
 and remains so during the first lymphocyte becomes the most numerous cell

and remains so during the first 4 postnatal years. In blood of newborns is sign by and CD4+ (helper/inducer phenotype) T-cell subsets

in blood of newborns is significantly higher than in adults. • In the newborn, approximately 15 percent of lymphocytes have immunoglobulin on their surface, with all immunoglobulin (7). their surface, with all immunograbulin (Ig) isotypes represented.

- The term newborn has reduced mean plasma levels (<60% of adult levels) of factors The term in and XII, prekallikrein, and high-molecular-weight kininogen. II, IX, X, XI, and XII, prekallikrein, of features of the plasma concentration of features.
- II, IX, A, the plasma concentration of factor VIII is similar and von Willebrand in contrast, the plasma concentration of factor VIII is similar and von Willebrand factor is increased compared to older children and worts.

### onic Hemoglobins (AllMS Question):

Laronic Her	noglobilis (Alline da	ootion).	No. 1 and 1
TI DI YOU	Chain Composition	Primarij Stat	
	282	Yolk sac	<5-6 weeks
u'a.	2:2	Yolk sac	4-13 weeks
11,31 2	C2 Y2	Yolk sac	4-13 weeks
٠,١,١	(2;2	Liver	Farly, 53-95% at term
٠, ١٢	α2 β2	Marrow	9 weeks, 5-45% at term
W A	(C- P-		

- . The  $\zeta$  -to-a-globin switch precedes the  $\epsilon$ -to- $\gamma$ -globin switch as the liver replaces the yolk sac as the main site of erythropolesis.
- Hgb A<sub>2</sub> has not been detected in fetuses.
- . Normal adult levels of Hgb A<sub>2</sub> are achieved by 4 months of age (\*).
- . Decreased levels of Hgb F at birth are found in trisomy 21 (\*).
- By 1 year of age the i antigen is undetectable, and the ABH antigens increase to adult evels by age 3 years.
- · The life span of the red cells in the newborn infant is shorter than that of red cells in
- The average of several studies of mean half-life of newborn red cells is 60 to 80 days (\*).

### White Blood Cells:

- The absolute number of neutrophils in the blood of term and premature infants usually is greater than that found in older children.
- In term infants, opsonic activity is normal for Staphylococcus aureus, but it is low for yeast and Escherichia coli.
- Diminished opsonic antibody is associated with group B streptococcal infection and represents one risk factor for neonatal infection.
- In premature infants, opsonic activity is low for S. aureus and Serratia marcescens, but is normal for Pseudomonas aeruginosa.
- \* Complement components appear in fetal blood before 20 weeks' gestation and increase markedly during the third trimester.
- The absolute number of CD3+ and CD4+ (helper/inducer phenotype) T-cell subsets in blood of newborns is higher than in adults. (\*).
- This is a result of an increased total lymphocyte count in neonates (and older children)
- There is a trend toward increased CD4 and decreased CD8 lymphocytes in newborns and children, resulting in an increased CD4:CD8 ratio.



 In spite of this, T-cell suppressor activity may be increased in newborns. In spite of this, T-cell suppressor activity may
 In spite of this, T-cell suppressor activity may
 Humoral (B-cell) immunity also develops early in gestation, but it is not fully active
 Humoral (B-cell) immunity also develops early in gestation, but it is not fully active
 Humoral (B-cell) immunity also develops early in gestation, but it is not fully active
 Humoral (B-cell) immunity also develops early in gestation, but it is not fully active Humoral (B-cell) immunity also develops early in gestated, the limit fully active humoral (B-cell) immunity also develops early in gestated.

Humoral (B-cell) immunity also develops early in gestated, approximately 15 percent of lymphocytes have until after birth. In the newborn, approximately 15 percent of lymphocytes have until after birth. In the insurface, with all Ig isotypes represented.

until after birth. In the newborn, application of their surface, with all Ig isotypes represented.

Coagulation:

• The term newborn has reduced mean plasma levels (<60% of adult levels) of factors

• The term newborn has reduced mean plasma levels (<60% of adult levels) of factors

The term newborn has reduced mean phonolecular-weight kininogen.

II, IX, X, XI, XII, prekallikrein, and high-molecular-weight kininogen. II, IX, X, XI, XII, prekallikrein, and ringh.

In contrast, the plasma concentration of factor VIII is similar and von Willebrand

In contrast, the plasma concentration of older children and adults.

factor is increased compared to that of older children and adults. factor is increased compared to that of the functional tests (prothrombin and partial of the lower levels of factors, the functional tests (prothrombin and partial of the lower levels of factors, the functional tests (prothrombin and partial of the lower levels of factors, the functional tests (prothrombin and partial of the lower levels of factors) and partial of the lower levels of factors, the functional tests (prothrombin and partial of the lower levels of factors) and partial of the lower levels of factors and partial of the lower levels of factors. In spite of the lower levels of factors, the relief compared to adult normal values.

Thromboplastin times) are only slightly prolonged compared to adult normal values.

Near-adult values are achieved for most components by 6 months of age.

Near-adult values are achieved for the final gamma.
 Factors II (prothrombin), VII, IX, and X require vitamin K for the final gamma.

glutamyl carboxylation step in their synthesis.

• These factors decrease during the first 3 to 4 days after birth. This fall may be These factors decrease during the first sectively preventing classic, early occurring lessened by administration of vitamin K, effectively preventing classic, early occurring (first few days after birth) hemorrhagic disease of the newborn.

A hemorrhagic diathesis also may occur later, 2 to 12 weeks after birth, as a result of lack of vitamin K, and is called late hemorrhagic disease of the newborn or acquired prothrombin complex deficiency.

The ettology of the vitamin K lack is unclear but may result from poor dietary intake, particularly related to breast feeding, alterations in liver function with cholestasis and decreased vitamin K absorption, or a toxic or infectious impairment of hepatic utilization. Unfortunately, intracrania 1 hemorrhage frequently is the presenting event in this condition.

The current recommendation of the American Academy of Pediatrics suggests that vitamin K1, 0.5 to 1 mg, be administered intramuscularly at birth.

 Significant bleeding occurs more often in low-birth-weight infants than in term newborn infants. Increased capillary fragility is frequently found in premature infants in the first 2 days after birth and is not associated with thrombocytopenia.

• The levels of proteins C and S, which are vitamin K-dependent, as well as antithrombin and heparin cofactor II, are low in the newborn.

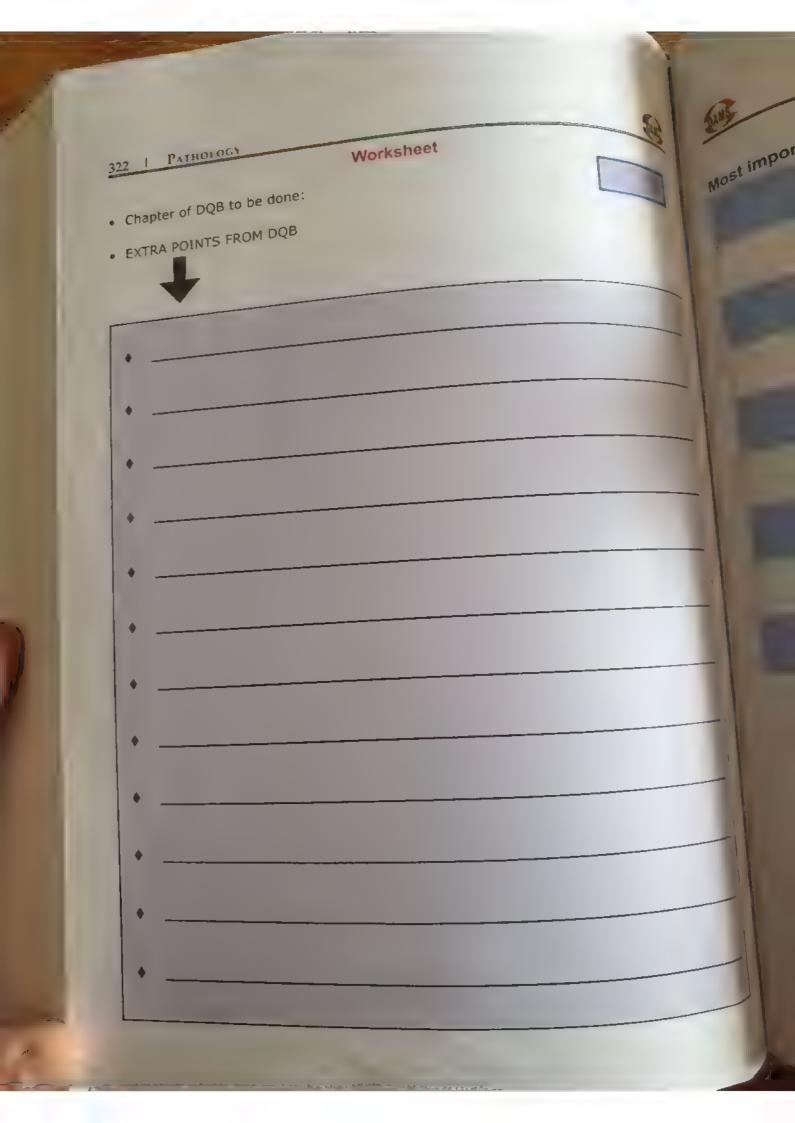
# Haematological Effects of Maternal Drugs on Fetus and Newborn:

Contract of the last of the la		ags of retus and Newborn.		
Antiretroviral agents in	T. Breeze		Mal	
combination Aspirin	Decreased hemoglobin	Established	Unknown only seen with combination of zidovudine, lamivudine + nelfinavir.	
	Bleeding, kernicterus	Established; potential	Interference with platelet function.	
Diazoxide	Bleeding		Displacement of bilirubin from albumin.	
Nalidixic acid	Hyperbilirubinemia	Questionable	Thrombocytopenia	
	- The title	Potential	Oxidant damage to hemoglobin	

1 1000	Hyperbilicubinemia	Potential	Oxidant damage to hemoglobin
pre vicin (Dilantin/phenobarbital)	Bleeding	Suspected	Depletion of vitamin K-dependent coagulation factors by hepatic enzyme induction and factor degradation.
Riftimp in sontazid	Bleeding	Suspected	Depletion of vitamin K-dependent coagulation factors.
<sub>Rullenam</sub> des	Kernicterus	Established	Displacement of bilirubin from albumin.
le.	Bleeding	Suspected	Thrombocytopenia
<sub>varfarin (Coumadin)</sub>	Bleeding	Established	Known depletion of vitamin  K-dependent coagulation factor by blocking carboxylation.

### Hematology In Pregnancy:

- . Maternal blood volume increases by an average of 40 to 50 percent above the nonpregnant level.
- . P.asma volume begins to rise early in pregnancy, with most of the escalation taking place in the second trimester and prior to week 32 of gestation.
- Red cell mass increases significantly beginning in the second trimester and continues to expand throughout pregnancy, but to a lesser extent than plasma volume.
- Erythropoietin levels increase throughout pregnancy, reaching approximately 150 percent of their prepregnancy levels at term.
- The overall effect of these changes in most women is a slight drop in hemoglobin concentration, which is most pronounced at the end of the second trimester and slowly improves approaching term.
- During labor and the early puerperium, there is a rise in the leukocyte count. Leukocytosis appears to be linearly related to the duration of labor.
- The levels of some plasma proteins also increase during pregnancy.
- In particular, C-reactive protein concentration is higher in pregnant women and rises
- Erythrocyte sedimentation rate (ESR) rises during pregnancy, and is affected by both hemoglobin concentration and gestational age.
- The rise in ESR during pregnancy, in large part a result of an increase in levels of plasma globulins and fibrinogen, makes its use as a marker of inflammation difficult.
- The levels of many of the procoagulant factors increase during pregnancy whereas activity of the fibrinolytic system diminishes in preparation for the hemostatic
- Plasma levels of von Willebrand factor (VWF), fibrinogen, and factors VII, VIII, and X all increase markedly, whereas factors II, V, IX, and XII are essentially unchanged
- Levels of protein C and antithrombin remain stable throughout pregnancy whereas total and free protein S fall with increasing gestational age.
- \* Fibrinolysis is also impaired by increases in plasminogen activator inhibitors I and II, the latter a product of the placenta.





HEMATOLOGY IN NEWBORN AND PREGNANCY | 323

### **Active Recalls**

most important facts to be remembered



# RED BLOOD CELL AND DISORDERS OF IRON METABOLISM

# CONCEPTS

Soncept 14.1: Red Blood Cell and Disorders of Iron Metabolism Concept 14.1: Red Blood Cell and Disorders of Iron Metabolism

Concept 14.1: Red Blood Cell and Disorders and differences between other

Learning Objectives: Iron metabolism, IDA features and differences between other

D/D. Hemochromatosis Time Needed 30 min 2nd reading CFU MK PROERYTHROBLAST CFU-E BASOPHILIC ERYTHORBLAST POLYCHROMATOPHILIC ERYTHROBLAST ORTHOCHROMATIC ERYTHROBLAST RETICULOCYTE RED CELL

Fig 141

Hemoglobin's first formed at the stage of proerythroblast but at this stage it cannot be stained by Giemsa and can only be seen on electron microscoppy. (\*)

The first faint blush of Hb can be seen at the stage of Intermediate normoblast/
Polychromatophilic normoblast. (\*)

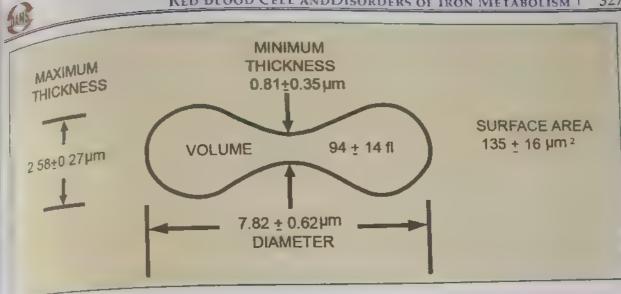


Fig. 14.2

- Historically, membrane proteins were thus first characterized by whether they were stanable by protein-binding or carbohydrate-specific dyes.
- . Now, however, they are classified on the basis of their relationship to the membrane or their functions.
- One common classification of membrane proteins comprises the categories of integral membrane proteins and peripheral membrane proteins.
- Integral membrane proteins are most often globular and amphipathic; in their folded, three-dimensional form, they have distinct hydrophobic and hydrophilic domains. Of the major Coomassie-stainable proteins, only bands 3, 4.5, and 7 are integral membrane proteins.
- The two predominant erythrocyte transmembrane proteins are glycophorin A (GPA) (most common integral protein) (\*) and the anion channel (AE1, formerly known as Band 3).
- The most abundant of the peripheral/cytoskeletal proteins are those that make up the so-called spectrin-actin cytoskeletal complex (\*).
- Erythrocytes have an abundant and highly active water channel protein, aquaporin-1, which contributes as much as 85% of the osmotic water permeability pathway.

# In disease, abnormality in the red cell picture stems from four main causes:

- Approximal erythropolesis that may be effective or ineffective
- 1 2. Inadequate haemoglobin formation
  - Damage to, or changes affecting, the red cells after leaving the bone marrow, including the effects of reduced or absent splenic function
- Attempts by the bone marrow to compensate for anaemia by increased erythropoiesis.

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These processes result, respectively, in the following abnormalities of the

Cells:
Increased variation in size (anisocytosis) and shape (porkilocytosis) and punctate basophilia, red cells:

- Reduced or unequal haemographic content (hypochromasia, anisochromasia, or dimorprisa), Reduced or integral national contraction, elliptocytosis, or fragmentation (schistocytosis) in prosession specific and a variable number of certain specific
- Spher Catalan inegular contraction, elliptocytosis, or range number of certain specific per language of Pappenberner bodies, Howell Tolly bodies, and a variable number of certain specific per language and spherocytes). (target cells, acanthocytes, and spherocytes).
- Signs of immaturity (polychromasia and erythroblastaemia)

A clear explanation for the mechanism of red cell senescence remains elusive. It may be that tumped a clear explanation for the mechanism of red cell senescence remains elusive. It may be that tumped a combination of the abnormalities described as the combination of the c A clear explanation for the mechanism of red cell series combination of the abnormalities described in erythrocyte aging and destruction results from a combination of the abnormalities described in erythrocyte aging and destruction results from a combination of the abnormalities described in erythrocyte aging and destruction results from a considered phenomenon. Contrary to long the preceding paragraphs, or from some as yet unrecognized phenomenon. Contrary to long the preceding paragraphs, or from some as yet unrecognized phenomenon. The role of membrane the preceding paragraphs. the preceding paragraphs, or from some as yet united graphs. The role of membrane corresponding possibility relates to charge process. It probably is not due to enzyme or energy depletion. The role of membrane corresponding possibility relates to charge a terations also has not been documented. The one intriguing possibility relates to charges in Rec a terations also has not been documented. The one introduced serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phosphatidyl serine exposure on the external membrane phospholipid asymmetry associated with phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the external membrane phospholipid asymmetry as a series of the ext membrane phospholipid asymmetry associated with property of how cells are removed from the circulation, bilayer. This mechanism would fit into a general concept of how cells are removed from the circulation,

Under normal conditions approximately 80 to 90% of normal erythrocyte destruction occurs without release of hemoglobin into plasma.

Because of this fact, the major part of the destructive process is considered to be extravascular, within macrophages of the spleen and, to a lesser extent, the liver and bone marrow. Only 10 to 20% of normal destruction occurs intravascularly,

### Haptoglobins:

Haptoglobins are a family of  $\alpha$ ,-glycoproteins that bind hemoglobin.

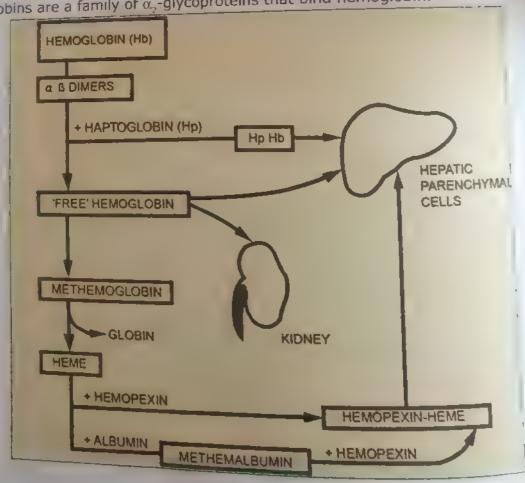


Fig. 14.3

The tetrameric molecule resembles certain immunoglobulins in that it has two light ( $\alpha$ ) The tender two heavy (β) chains linked in humans by disulfide bonds.

chains synthesized as a single polypeptide chain that is cleaved posttranslationally the endonlasmic reticulum to generate its conditionally Haptoglobility that is cleaved posttranslationally within the endoplasmic reticulum to generate its α and β subunits Transcriptional activity of the haptoglobin gene is promoted by interleukin-1, interleukin-6, and glucocorticoids of the nopted of the acute-phase response to systemic inflammation and related physiologic as a part of the reby explaining why haptoglobin levels are increased with inflammation. An increased haptoglobin level is recognized as a nonspecific sign of disease with much the same significance as an accelerated sedimentation rate.

### Pathways for the Disposal of Hemoglobin in Plasma:

Hemoglobin freely dissociates into  $\alpha\beta$  dimers. These are bound by haptoglobin with subsequent removal of the hemoglobin-haptoglobin complex by hepatic parenchymal cells. Hemoglobin in excess of the haptoglobin-binding capacity circulates as the unbound (free) protein. In this form it is partially removed by hepatic cells, but it may also follow two other pathways; it may be excreted by the kidney or oxidized to methemoglobin, from which heme is easily dissociated. Heme is initially bound to hemopexin, which transports it to the hepatic parenchymal cell. Heme may also be bound nonspecifically by aroumin, forming methemalbumin. This complex probably transfers its heme to hemopexin as the latter becomes available.

### iron Deficiency Anemia:

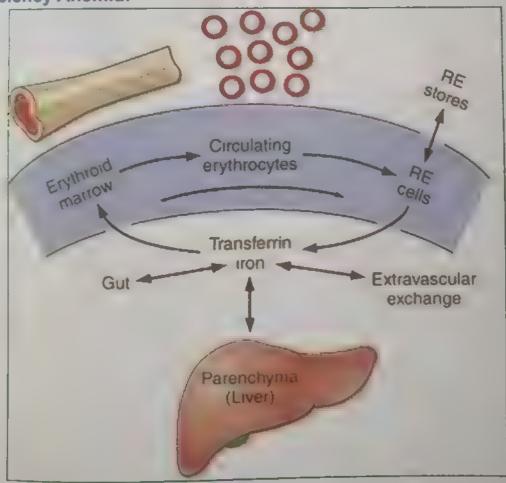


Fig. 14.4

HOLUG	Normal	Negative tron balance	deficient erythropoiesis	deficiency anemia
Iron stores Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (µg/L)	50-200	∠20	<15	<15
TIBC (µg/dL)	300-360	1 >360 ·	>380	>400
SI (µg/dL)	50-150	NL	· <50	<30
Saturation (%)	30-50	NL	∠20	<10
Marrow sideroblasts (%)	40-60	NL	<10	<10
protoporphyrin (µg/dL)	30-50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/ hypochromic

Fig. 14.5

### Course of their Deficiently

Increased Demand for Iron

Rapid growth in infancy or adolescence

Pregnancy

Erythropoietin therapy

Increased Iron Loss

Chronic blood loss

Menses

Acute blood loss

Blood donation

Phlebotomy as treatment for polycythemia vera

Decreased Iron Intake or Absorption

Inadequate diet

Malabsorption from disease (sprue, Crohn's disease)

Malabsorption from surgery (postgastrectomy)

Acute or chronic inflammation



### Clinical Features:

When anemia develops rapidly, shortness of breath, tachycardia, dizziness or faintness When arising from a sitting or recumbent posture), and extreme fatigue

In chronic anemia, only moderate dyspnea or palpitation may occur, but in some patients, congestive heart failure, angina pectoris, or intermittent claudication can be the presenting manifestation.

Heart murmurs are a common cardiac sign associated with anemia. They usually are systolic in time and best heard in the pulmonic area.

The pallor associated with anemia is best detected in the mucous membranes of the mouth and pharynx, the conjunctivae, the lips, and the nail beds.

. In the hands, the skin of the palms first becomes pale, but the creases may retain their usual pink color until the Hb concentration is <7 g/dl (\*).

A distinctly sallow color implies chronic anemia. (\*).

- · A lemon-yellow pallor suggests pernicious anemia, but it is observed only when the condition is well advanced. (\*).
- Definite pallor associated with mild scleral and cutaneous icterus suggests hemolytic anemia. (\*).
- Marked pallor associated with petechiae or ecchymoses suggests more generalized bone marrow failure due to acute leukemia, aplasia, or myelodysplastic syndromes.
- The nails may lose their luster, become brittle, and break easily.
- · This finding is especially noticeable in chronic iron deficiency anemia, in which the nails may actually become concave instead of convex (koilonychia).
- Approximately 20% of such patients have flame-shaped hemorrhages, hard exudates, cottonwood spots, or venous tortuousness affecting the retina.

 The craving to eat unusual substances, for example, dirt, clay, ice, laundry starch, salt, cardboard, and hair, is a classic manifestation of iron deficiency and is usually cured promptly by iron therapy (PICA).

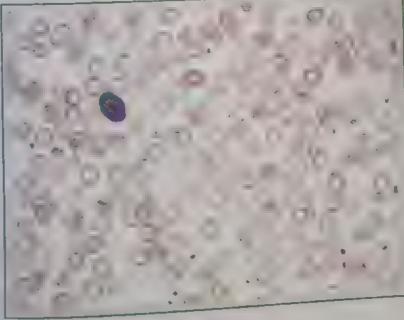


Fig. 14.6



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### tial Diagnosis of Microcytic Anemia:

		Inflammation	Thalassemia	Sideroblastic Anemia
Tests	Iron Deficiency		Micro/hypo with	Variable
Smear	Micro/hypo	Normal micro/ hypo	targeting	
	1 -20	<50	Normal to high	Normal to high
St	<30	₹300	Normal	Normal
TIBC	>360	10-20	30-80	30-80
Percent saturation	<10		50-300	50-300
Ferritin (g.L)	<15	30-200		
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with beta thalassemia; can be normal with alpha thalassemia	Normal

#### Serum Ferritin.

Most sensitive and specific test for diagnosis of iron deficiency anemia

It decreases even before the appearance of anemia.

Correlates with body iron stores (1  $\mu$ g/L = 10 mg storage iron).

Levels ess than 12 µg/L are highly specific for diagnosis of iron deficiency anemia.

Not sattable for diagnosing iron deficiency anemia in patients with concomitant inflammation, neoplastic or aver disorders

### **Most Commonly Asked Questions:**

- 1. Most important finding of iron deficiency anemia- anisocytosis (earliest also).
- 2 First sign of improvement after iron therapy- improvement in symptoms.
- 3. Diagnosis of iron deficiency in pregnancy- serum ferritin.

### Once the Diagnosis of Iron-Deficiency Anemia and its Cause is Made, There are Three Major Therapeutic Approaches:

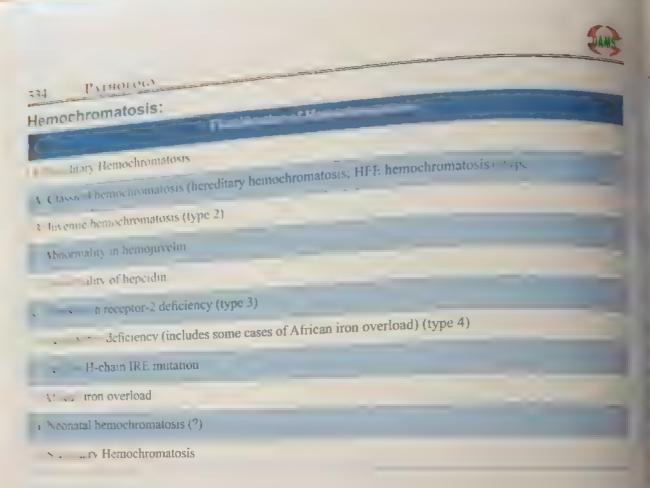
- 1. Transfusion therapy is reserved for individuals who have symptoms of anemia, cardiovascular instability, continued and excessive blood loss from whatever source, and require immediate intervention. The management of these patients is less related to the iron deficiency than it is to the consequences of the severe anemia. Not only do transfusions correct the anemia acutely, but the transfused red cells provide a source of iron for reutilization, assuming they are not lost through continued bleeding.
- 2. In the asymptomatic patient with established iron-deficiency anemia, treatment with oral iron is usually adequate.



ne Tablet (Iron Content), mg	Elixir (Iron Content), mg in 5 ml
	300 (60)
ate 325 (65) 195 (39)	90 (18)
525 (105)	
325 (107)	
195 (64)	100 (33)
325 (39)	300 (35)
	*00 (100)
ide 150 (150)	100 (100)

Of the complications of oral iron therapy, gastrointestinal distress is the most prominent and is seen in 15-20% of patients. Typically, the reticulocyte count should begin to ncrease within 4-7 days after initiation of therapy and peak at 1-11/2 weeks.

- 1. Intravenous iron can be given to patients who are unable to tolerate oral iron; whose needs are relatively acute; or who need iron on an ongoing basis, usually due to persistent gastrointestinal blood loss.
- 2. Parenteral iron therapy may be indicated when the patient.
  - a. has severe iron deficiency anemia;
  - b. is unable to tolerate iron compounds given orally;
  - c. repeatedly does not heed instructions or is incapable of accepting or following them;
  - d. loses iron (blood) at a rate too rapid for the oral intake to compensate for the loss, such as in hereditary hemorrhagic telangiectasia;
  - e. has a disorder of the gastrointestinal tract, such as ulcerative colitis, in which symptoms may be aggravated by iron therapy;
  - f. is unable to absorb iron from the gastrointestinal tract;
  - 9. is unable to maintain iron balance on treatment with hemodialysis; or
  - h. has functional iron deficiency because of concurrent treatment with erythropoletin (e.g., in the anemia of renal failure, in the anemia of inflammation, or for autologous blood donation).



#### Pathophysiology:

Normal humans absorb and lose approximately 1 mg of iron each day.

I sera absorption of iron increases when iron deficiency occurs, then drops to 1 mg/ day after iron deficiency is corrected.

-

1901

In iron-loaded subjects with hemochromatosis, iron absorption usually is >2 mg/day at a time when iron absorption should have decreased to nearly zero.

The progressive accumulation of iron increases plasma iron, saturation of transferrin, and results in a progressive increase of plasma ferritin

### HFE gene (High FE- High iron gene):

The HFE gene is located on the short arm of chromosome 6, approximately 4 megabases

The HFE gene is structurally somewhat similar to other HLA class I-like genes.

The HEF gene s composed of seven exons, of which the first six exons encode for the

The seven exons of HFE result in formation of a messenger RNA transcript that is project which consider the 24.) In size. This in turn results in the synthesis of the HFE

The most common iron-loading mutation of HFE (C282Y) is caused by a mutation of one nucleotide base (C110). mutation of one nucleotide base (845G · A) in exon 4 of the HFE gene

of the known mutations of the HFE gene, 16 are missense mutations that result in of the kind of the normal amino acid by another.

The HEIRS Study (HEmochromatosis and IRon Overload Screening Study) is the The HEIRS of the prevalence of mutations of HFE and of serum iron tests.

# Clinical Features:

- Chinical Symptoms are often nonspecific and include lethargy, arthralgia, change in skin oss of libido, and features of diabetes mellitus.
- negative heart failured as arrhythmias congestive heart failured as arrhythmias ar tes, cardiac arrhythmias, congestive heart failure, loss of body hair, test cuiar and jound ce are prominent in advanced disease.
- . Tran or promise pigmentation is the most common physical examination abnormal ty
- , the liver is usually the first organ to be affected, and hepatomegaly is present in more than 95% of symptomatic patients (\*).
- . -epotoce rurar carcinoma develops in about 30% of patients with cirrhosis, and it is me most common cause of death in treated patients—hence the importance of early diagnosis and therapy.
- The maracteristic metallic or slate-gray hue is sometimes referred to as bronzing and results from increased melanin and iron in the dermis.
- Pamentation usually is diffuse and generalized, but it may be more pronounced on the face neck, extensor aspects of the lower forearms, dorsa of the hands, lower legs, and genital regions, as well as in scars.
- · The joints of the hands, especially the second and third metacarpophalangea Acts are usually the first joints involved, a feature that helps to distinguish the Chandracalcinosis associated with hemochromatosis from the idiopathic form.
- \* The most common cardiac manifestation is congestive heart failure, which occurs 1 35% t 10% of young adults with the disease, especially those with juvenile hemochromatosis.
- · Hypogonadism occurs in both sexes and may antedate other clinical features.
- Manufestations include loss of libido, impotence, amenorrhea, testicular atrophy, gynecomiastia, and sparse body hair. These changes are primarily the result of decreased production of gonadotropins due to impairment of hypothalamic-pituitary function by iron deposition.
- Adrenal insufficiency, hypothyroidism, and hypoparathyroidism are rare manifestations.

	Andreas de la constitución de la c	THE RESERVE AND PERSONS NAMED IN			
Determination	Normal	Symptomatic Hemochroma- tosis	Homozygotes with Early. Asymptomatic Hemochromatosis	Heterozygotes	Alcoholic Liver Disease
Plasma iron, mmoi/l.	9-27 (50-150)	32-54 (180-300)	Usually elevated	Elevated or normal	Often elevate
(mg/dL) Total iron-binding canacity, mmol/L (mg/	45-66 (250-370)	36-54 (200-300)	36-54 (200-300)	Elevated or normal	45–66 (250–370)
dl ) Transferrin saturation,	22-46	50-100	50–100	Normal or elevated	27-60
serum ferntin, mg.L		900-6000	200-500	Usually <500	10-500
Meo	20250				
Women	15–150				
Liver from, mg/g dry wt	300-1400	6000-18,000	2000-4000	300–3000	300-2000
Hepatic iron index	<1.0	>2	1.5–2	<2	<2

The most common laboratory abnormalities in subjects with hemochromatosis are elevations of serum iron concentration, the percent saturation of transferrin, and the serum ferritin concentration.

The next most common laboratory abnormality in hemochromatosis patients is elevation of serum alanine aminotransferase and aspartate aminotransferase.

#### Treatment:

- The therapy of hemochromatosis involves removal of the excess body iron and supportive treatment of damaged organs.
- Iron removal is best accomplished by weekly or twice-weekly phlebotomy of 500 mL
- Each milliliter of packed red cells contains approximately 1 mg of iron.
- Thus, the removal of 500 mL of blood with a hematocrit of 40 percent removes
- As the red cell mass is restored to its prephlebotomy size, iron is mobilized from the
- When the stores have been exhausted the signs of Iron deficiency develop, and this
- is the endpoint of the initial part of the phlebotomy program. The pat ent is then followed and a schedule of maintenance phlebotomies is established with the frequency of phlebotomies to illustrate level, the
- with the frequency of phlebotomies tailored to maintain the serum ferritin level, the best indicator of body stores, below 100 ng/mL. • Chelating agents such as deferoxamine, when given parenterally, remove 10–20 mg
- such as deferoxamine, when given parenterally, remove to Subcutaneous infusion of defermine that mobilized by once-weekly phlebotomy. • Subcutaneous infusion of deferoxamine using a portable pump is the most effective

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Transferrin saturation

Treatment

### Active Recalls

Most important facts to be remembered

Serum iron
Serum ferritin
FIBC



# MEGALOBLASTIC ANEMIA

## CONCEPTS

Ecocept 15.1 Megalobiastic Anemia



### Concept 15 1 Megaloblastic Anemia

Learning Objectives: B12 and folic acid deficiency anemia, source, causes and metabolism

#### Time Needed

1* reading	30 min
2 <sup>nd</sup> reading	15 min

### Megaloblastic Anemia

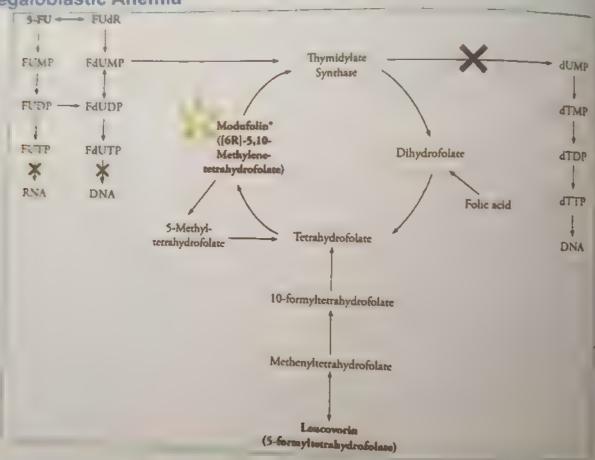


Fig. 15.1

### auses of viceatomiastic A

Cobalamin deliciency or abnormalities of cobalamin metabolism (see Tables 105-3 and 105-4)

Lolate deficiency or abnormalities of folate metabolism (see Table 105-5)

Therapy with antifolate drugs (e.g., methotrexate)

Independent of either cobalamin or folate deficiency and retractory to cobalamin and folate therapy: Some cases of acute mycloid leukemia, inyclodysplasia

Therapy with drugs interfering with synthesis of DNA [e.g., cytosine arabinoside,

hydroxyurea, 6-mercaptopurine, azidothymidine (AZT)] Orotic aciduria (responds to uridine)

Thiamine-responsive

1	T (Delamate-Di	
	Source	Function
otem <sub>innsic</sub> factor	Gastric parietal cells	Promotes absorption uptake of cobalamin by tleum
	Probably all cells	Promotes uptake of cobalamin by cells
nscopalamin atocorna	Exocrine glands, phagocytes	Helps dispose of cobalamin analogues (?)

Folate deficiency typically evolves rapidly, and it is often associated with other deficiencies and with alcohol abuse.

and with a cobalamin deficiency has a slow onset usually measured in years, and it in contrast, to be a purer deficiency state because of the frequent restriction of malabsorption to cobalamin alone.

# Megaloblastic anemia is a panmyelosis:

- The common feature of all megaloblastic anemias is a defect in DNA synthesis that affects rapidly dividing cells in the bone marrow.
- . A conditions that give rise to megaloblastic changes have in common a disparity n the rate of synthesis or availability of the four immediate precursors of DNA: the geoxyr bonucleoside triphosphates (dNTPs) — dA (adenine) TP and dG (guanine) TP purines), dT (thymine) TP and dC (cytosine) TP (pyrimidines).
- . In deficiencies of either folate or cobalamin, there is failure to convert deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), the precursor of dTTP .
- This is the case because folate is needed as the coenzyme 5, 10-methylene-THF polyglutamate for conversion of dUMP to dTMP; the availability of 5, 10-methylene-THE s reduced in either cobalamin or folate deficiency.
- An a ternative theory for megaloblastic anemia in cobal-amin or folate deficiency is misincorporation of uracil into DNA because of a buildup of deoxyuridine triphosphate (dJTP) at the DNA replication fork as a consequence of the block in conversion of dUMP to dTMP.

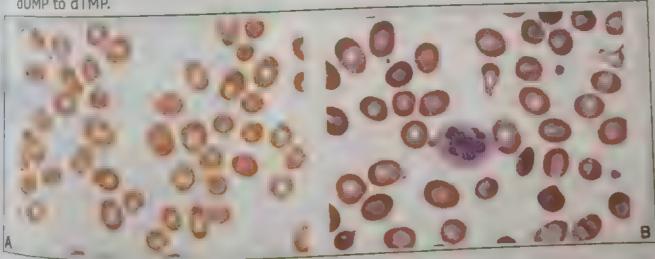


Fig. 15.2



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### Clinical Features:

- Epithelial Surfaces.
   At the many with mext most frequently affected tissues are the epithelial ce
- At the many the next most frequency intestine and the respiratory, utinary, at as at the mouth stomach and small intestine and the respiratory, utinary, and female genital tracts. The cells show macrocytosis, with increased numbers of and female genital tracts. The cells and female genital tracts. The deficiencies may cause cervical smear abnormalities
- · Complications of Pregnancy. The gonads are also affected, and infertility is common in both men and management has been implicated as a second management.
- The gonads are also affected, find the deficiency has been implicated as a cause with either deficiency. Maternal foliate deficiency have been implicated as a cause of capalarmin deficiency have been in the capala with either denciency. Material rolling and cobalamin deficiency have been implicated prematurity, and both foliate deficiency and cobalamin deficiency have been implicated n recurrent fetal loss and neural tube defects, as discussed below.
- Neural Tube Defects.
- By a supplements at the time of conception and in the first 12 weeks of pregnance ecce by around 70% the incidence of neural tube defects (NTDs) (anencepha) · · · convelocele, encephalocele, and spina bifida) in the fetus. Most of the total effect can be achieved by taking folic acid, 0.4 mg daily at the time of conception.
- Cardiovascular Disease.
- The green with severe homocystinuria (blood levels > 100 μmol/L) due to deficiency of one of three enzymes, methionine synthase, MTHFR, or cystathionine synthase, have ascular disease, e.g., ischemic heart disease, cerebrovascular disease, or pulmonary embolus as teenagers or in young adulthood.
- Neurologic Manifestations.
- · Cobalamin deficiency may cause a bilateral peripheral neuropathy or degeneration (demyelination) of the posterior and pyramidal tracts of the spinal cord and, less requently, optic atrophy or cerebral symptoms.
- Neuromyelopathic symptoms are the most common neurologic features of cobalance
- · Far est neurological sign due to cobalamin deficiency is said to precede other se progress findings by months loss of position sense in second toe and oss of vibration sense for 256 Hz tuning fork; not 128 Hz fork.
- Earliest indicator of folate deficiency is a low serum folate.
- LDH1 and LDH2 are both increased- megaloblastic LDH1 > LDH2.

### **Laboratory Features:**

- Megaloblastic anaemia resulting from impaired DNA synthesis is characterised by the
   presence of the solution of the s presence of margatoblastic red cell precursors in the bone marrow and occasionally
- Megalobiasts have a characteristic chromatin pattern and increased cytoplasm as a result
   of asynchrony of cucy mand and increased cytoplasm as a result of asynchrony of Luciear and cytoplasmic maturation with a relatively immature nucleus
- for the degree of cytoplasm c haemogrobin sation. (sieve like chromatin) (\*). The morphologic hairmark is nuclear-cytoplasmic dissociation, which is best
  appreciated in precursor colleges to the control of the cont appreciated in precursor cells in the bone marrow aspirate.

The delay in nuclear maturation caused by delay in DNA synthesis resulting from lack of vitamin B<sub>12</sub> or folate is also seen in all lineages, particularly granulocytic marrow of vitalism big and metamyelocytes and polylobed neutrophils with increased lobe precurs well as number of nuclear segments.

In severe pernicious anaemia a progressive increase in mean red cell volume (MCV) up to 130 fl occurs, with oval macrocytes, poikilocytes, and hypersegmentation of neutrophils (greater than 5% with more than 5 nuclear lobes).

The mean platelet volume is decreased, and there is increased platelet anisocytosis, as detected by the platelet distribution width (PDW).

The MCV falls to 110-120 fl as megaloblastic change advances. Howell-Jolly bodies and basophilic stippling are seen in the red cells.

The functional pathophysiology of megaloblastic anemia is ineffective hematopolesis in an three hematopoietic cell lines; bone marrow hyperplasia is intense but reticulocytosis does not occur.

. Ineffect ve hematopoiesis causes a minor component of hemolytic anemias causing

LOW SETUM glutathione has been reported as the most significant metabolic predictor of anemia in cobalamin deficiency.

Concession	of Cabalamin Deliciency Sufficiently Severe to Cause Management
iutritional	Vegans
falabsorption	Pernicious anemia
× IIC 134525	(ongenital absence of intrinsic factor or functional abnormality Total or partial gastrectomy
est na leataises	Intestinal stagnant loop syndrome: jejunal diverticulosis, ileocolic fistula, anatomic blind loop, intestinal stricture, etc.  Ileal resection and Crohn's disease
	Selective malabsorption with proteinuria
	Tropical sprue
	Transcobalamin II deficiency
	Fish tapeworm

### Pernicious Anemia:

- Pernicious anemia (PA) may be defined as a severe lack of IF due to gastric atrophy.
- This usually shows atrophy of all layers of the body and fundus, with loss of glandular e ements, an absence of parietal and chief cells and replacement by mucous cells, a mixed inflammatory cell infiltrate, and perhaps intestinal metaplasia.

• The infiltrate of plasma cells and lymphocytes contains an excess of CD4 cells. The

antral mucosa is usually well preserved. Two types of IF immunoglobulin G antibody may be found in the sera of patients with

One, the "blocking," or type I, antibody, prevents the combination of IF to ileal mucosa. Whereas the "binding," or type II, antibody prevents attachment of IF to ileal mucosa. Type I occurs in the sera of >55% of patients and type II in 35%.

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- IF antibodies cross the placenta and may cause temporary IF deficiency in a newborn infant.
- Patients with PA also show cell-mediated immunity to IF.
- Parietal cell antibody is present in the sera of almost 90% of adult patients with PA but is frequently present in other subjects.
- Thus, it occurs in as many as 16% of randomly selected female subjects age >60 years.
- The parietal cell antibody is directed against the  $\alpha$  and  $\beta$  subunits of the gastric proton pump (H+, K+-ATPase).

#### **FIGLU Excretion Test:**

FIGIu (formiminoglutamate) is excreted in excessive amounts in folate deficiency. In this test 15 gm oral dose of histidine is given to the patient and the urinary excretion of FIGIL is measured spectro photo metrically.

#### Treatment:

- Megaloblastic anemia should never be empirically with folic acid alone unless vitamin B12 levels are normal.
- Folate deficiency is treated by 1 to 2 mg folic acid per day orally.
- The aims of vitamin B12 replacement therapy are correction of hematocrit to improve neurological abnormalities and to refill storage pools. Initial therapy consists of 1000 μg of hydroxycobalamin every day for one week. Then maintenance every 3 months.
- Patients of pernicious anemia require maintenance therapy for indefinite period.

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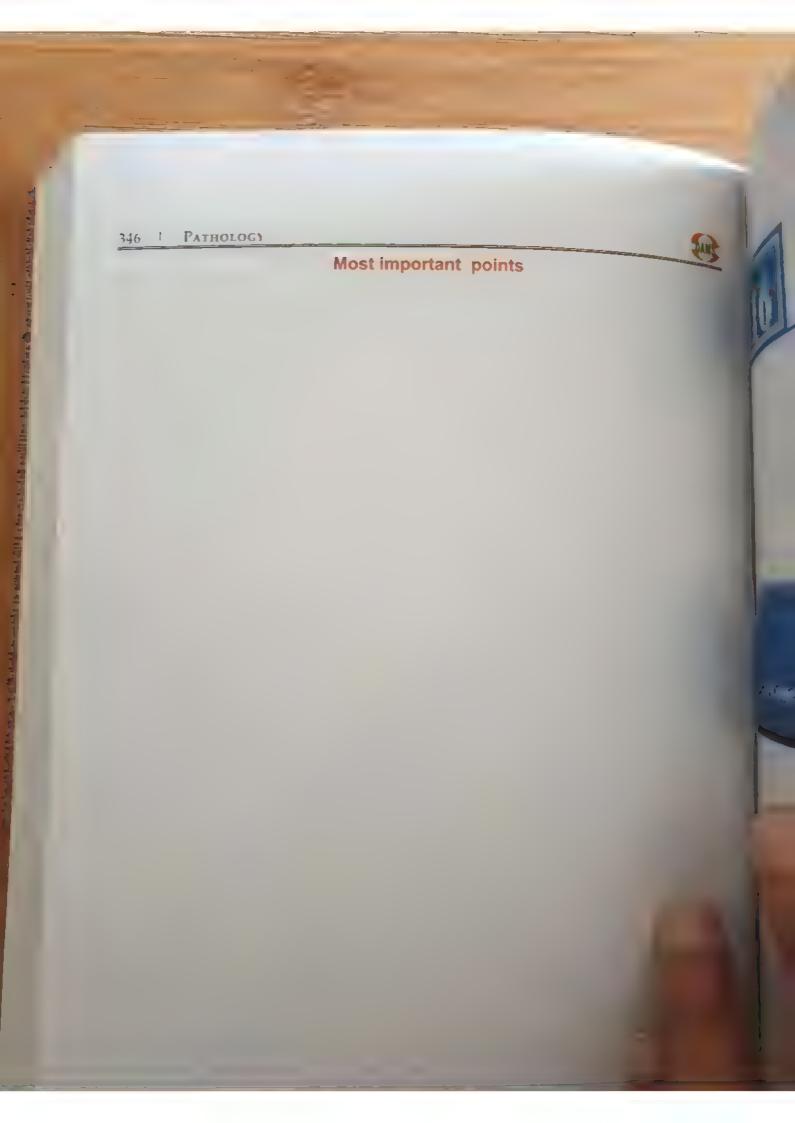
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### Worksheet

- . Chapter of DQB to be done:
- . EXTRA POINTS FROM DQB



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16 APLASTIC ANEMIA

# CONCEPTS

o Concept 16.1: Aplastic Anemia



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Concept: 16.1: Aplastic Anemia Concept: 16.1: Apiastic And folic acid deficiency anemia, source, causes and metabolism

### Time Needed

30 min | reading 15 min ?nd reading

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### Pancytopenia with Hypocellular Bone Marrow

Acquired aplastic anemia

Constitutional aplastic anemia (Fanconi's anemia, dyskeratosis congenita)

Some myelodysplasia

Rare aleukemic leukemia

Some acute lymphoid leukemia

Some lymphomas of bone marrow

#### Pancytopenia with Cellular Bone Marrow

Primary bone marrow Secondary to systemic diseases

diseases Systemic lupus erythematosus

Myelodysplasia Hypersplenism

Paroxysmal nocturnal B12, folate deficiency hemoglobinuria Overwhelming infection

Myelofibrosis Alcohol Some aleukemic Brucellosis

leukemia Sarcoidosis Myelophthisis Tuberculosis Bone marrow Leishmaniasis lymphoma

Hairy cell leukemia

### Hypocellular Bone Marrow ± Cytopenia

Q fever

Legionnaires' disease

Anorexia nervosa, starvation

Mycobacterium



### Etiologic Classification of Aplastic America

Acquired

Autoimmune

Drugs

See next table

Toxins

Benzens

Chlorinated hydrocarbons

Organophosphates

Viruses

Enstein-Barr virus

Non-A, -B, -C, -D, -E, or -G hepatitis virus

Human immunodeficiency virus (HIV)

Paroxysmal nocturnal hemoglobinuria

Autommune/connective tissue disorders

Eosmophilic fasciitis

Immune thyroid disease (Graves disease, Hashimoto thyroiditis)

Rheumatoid arthritis

Systemic lupus erythematosus

Thymoma

Pregnancy

latrogenic

Rad.atton

Cytotoxic drug therapy

Hereditary

Fanconi anemia

Dyskeratosis congenita

Shwachman-Diamond syndrome

Other rare syndromes

a		
B	11	A
А		87
	4	AM

1 11 ()		Inheritance	Mutated Gene	Reference
v. v. v. v. toperis	Emdings  Cerebellar atrophy and ataxia, plastic pancytopenia; monosomy 7- increased risk of	AD	Unknown	256-258
~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	Thrombocytopenia; absent or markedly decreased marrow megakaryocytes, hemorrhagic propensity; elevated thrombopoietin; propensity to progress to aplastic pancytopenia; propensity to evolve to clonal myeloid disease.	AR (compound heterozygotes).	МРІ	24, 260
NA San IV	Pre- and postnatal growth delay; dysmorphic facies; aplastic pancytopenia	AR (compound heterozygotes).	LIG4	261 263
rabow its syndrome	Intrauterine and post-partum growth failure; short stature; microcephaly; mental retardation; distinct dysmorphic facies; aplastic pancytopenia; increased risk of AML and ALL.	AR	Unknown	264 265
r clon breakage Freme	Microcephaly; dystrophic facies; short stature; immunodeficiency; radiation sensitivity; aplastic pancytopenia; predisposition to lymphoid malignancy.	AR	NBSI	266-267
deticular dysgenesis type of severe mmunodeficiency indrome.	Lymphopenia; anemia and neutropenia; corrected by hematopoietic stem cell transplantation.	XLR	Unknown	265 265
v i syndrome	Inhauter ne and post-partum growth ta tire incroeephaly. Calcite istic dysmorph classes that lended picties aplastic Lended picties aplastic VM.	AR	ATR (and RAD3 related gene), PCAT	2 % 1 27
	Radial/ulnar abnormalities; aplastic paneytopenia; increased	AD	Unknown	



Fanconi's Anemia: Fanconi anemia (FA) is an inherited chromosomal instability syndrome with a variable Fanconi alicination that includes congenital anomalies, progressive pancytopenia, and cancer susceptibility.

The diagnostic hallmark of FA is increased chromosomal breakage in response to DNA-damaging agents such as mitomycin C (MMC) or diepoxybutane (DEB).

There are currently 13 known FA subtypes (A, B, C, D1, D2, E, F, G, I, J, L, M and N).

With the exception of subtype B, which is X-linked recessive, all the other FA subtypes follow an autosomal recessive pattern of inheritance.

### hasical Findings I seminal I side I have I for

Skeletal.

Short stature.

Radial ray anomalies (thumbs, hands, radii).

Hip and spine anomalies.

Hyper gmentation (café au lait spots).

Hypop Imentation

Genitourinary.

Renal structural anomalies.

Hypogonadism.

(raniotacia)

Microcephaly

Ophtia mic anomalies (microphthalmia, epicanthal folds).

Our anomalies (external and middle ear anomalies, deafness).

Gastrointestinal malformations

Esophageal atresia or tracheoesophageal fistula

Imperforate anus

Cardiac malformations

 Growth hormone deficiency has been observed in some FA patients, and treatment with growth hormone improved growth in a subset of these patients.

 Additional endocrine disorders associated with Fanconi anemia include hypothyroidism with or without thyroid hormone-binding globulin (TBG) deficiency, abnormal glucose tolerance, and diabetes mellitus.

### Laboratory Features:

Blood counts and marrow cellularity are often normal until 5 to 10 years of age, when Pancytopenia develops over an extended interval.

The hematologic complications of FA typically present within the first decade of life. Early manifestations include moderate single or bilineage cytopenia with red cell macrocytosis.



Temorie:

Thrombacytepenia may precede the development of granulocytopenia and anemia,

Thrombacytepenia may precede the development of granulocytopenia and anemia,

Thrombacytepenia may precede the development of granulocytopenia and anemia, The marrow becomes hypocellular, and in vitro colony assays reveal a decrease in

Random chromatid breaks are present in myeloid cells, lymphocytes, and chorionic

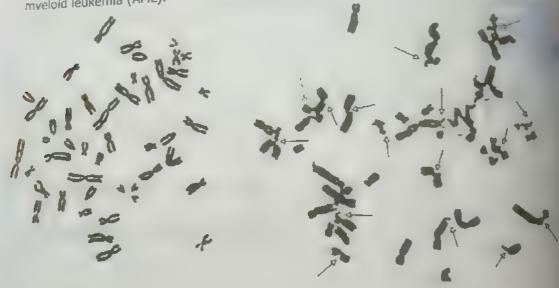
The diagnosis of Fanconi anemia is based on the demonstration of increased

the diagnosis of Fanconi anemia is book of DNA cross-linking agents, such as chromosomal breakage in the presence of DNA cross-linking agents, such as mitomycin C (MMC) or diepoxybutane (DEB). • The hypersensitivity of the chromosomes of marrow cells or lymphocytes to the latter

agent is used as a diagnostic test for this condition. agent is used as a diagnostic test of developing myelodysplasia (MDS) or acute

Patients with FA are at increased risk of developing myelodysplasia (MDS) or acute

mveloid leukemia (AML).



-MMC

+MMC

Fig. 16.1

# Chromosomal Breakage in Fanconi Anemia:

Peripheral blood lymphocytes from a Fanconi anemia patient were cultured without (left)

- Most patients with Fanconi anemia do not respond to ATG or cyclosporine but do Carcon with androgen preparations, often for as long as several years.
- Carrer surveillance and education plays an important role in the management of Fancon, anemia patients Physicians should counsel patients regarding established behavioral and environmental rick factorial should counsel patients regarding established benavioral and environmental risk factors associated with increased cancer risk.

Because of the increased risk of MDS and leukemia in patients with bone marrow Because syndromes, frequent complete blood counts and annual bone marrow aspirates and biopsies with cytogenetic analysis are recommended.

Hematopoietic stem cell transplantation is the only curative therapy for the hematologic manifestations of FA.

## Dyskeratosis Congenita:

- Dyskeratosis congenita (DC) is an inherited disorder characterized by lacey reticular pyskeration, nail dystrophy, and leukoplakia (the diagnostic triad).
- X-linked recessive (most common), autosomal dominant, and autosomal recessive inheritance patterns have been reported.
- , Patients exhibit a predisposition to bone marrow failure, malignancy, and pulmonary dysfunction.

### Clinical Features Associated with

Skin pigmentary abnormalities.

Nail dystrophy.

Leukoplakia.

Epiphora

Cognitive/developmental delay.

Pulmonary disease.

Short stature.

Dental caries/tooth loss.

Esophageal stricture.

Hair loss/gray hair/sparse eyelashes.

Hyperhidrosis.

Intrauterine growth retardation.

Gastrointestinal disorders.

Ataxia

A

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Hypogonadism/undescended testes.

Microcephaly.

Usethral stricture/phimosis.

Osteoporosis/aseptic necrosis/scoliosis.

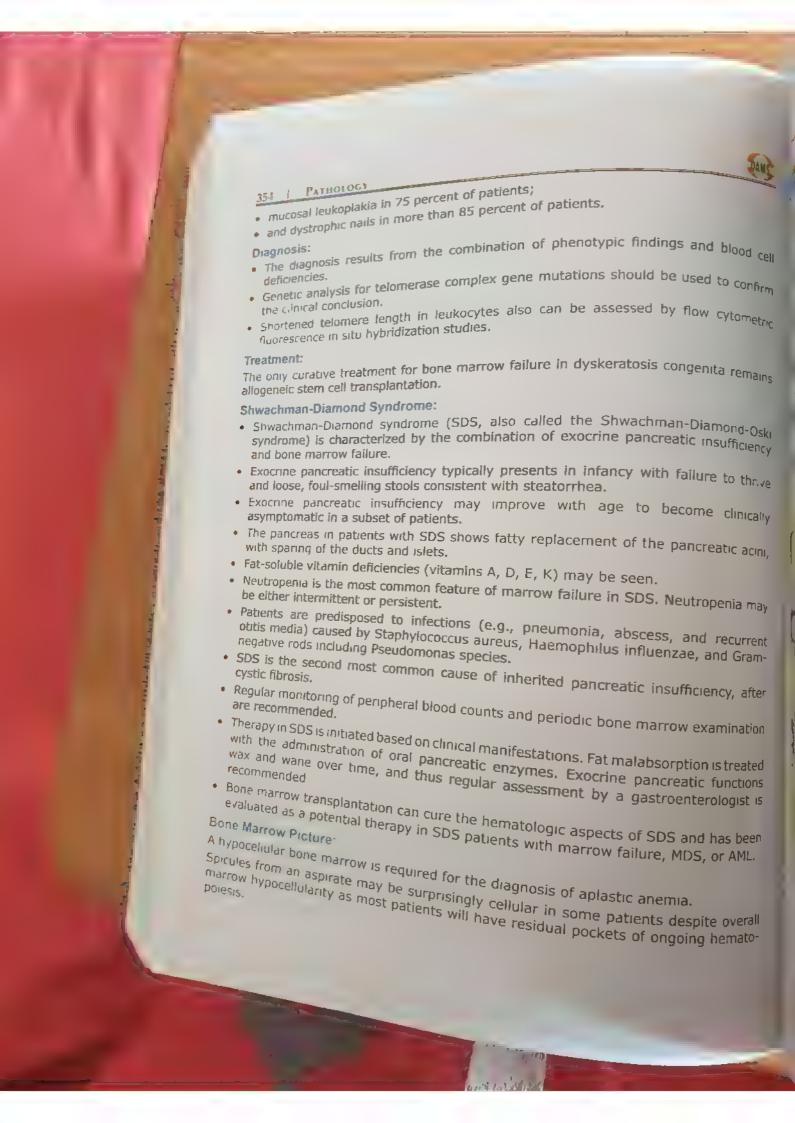
Deafness.

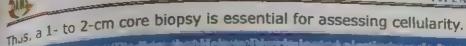
Bone marrow failure

Malignancy.

The cutaneous findings usually appear after 5 years of age and include.

- reticulated, tan to gray, hyperpigmented and hypopigmented cutaneous macules;
- alopecia of scalp, eyelashes, and eyebrows;
- adermatoglyphia (loss of dermal ridges on fingers and toes);
- hyperkeratosis of palms and soles;





Characteristic	Myelodysplastic Syndromes	Aplastic Anemia
	Usually increased or normala	Decreased
e mlarity D34 count	Normal to increased	Decreased
- ningis	-1-2	
legaloh astosis	Common	Common
yserythropoiesis	Common	Sometimes
inged sideroblasts	Common	Never
Avelopoiesis		
ncreased blasts	Common	Never
Megakaryocytes		
Dysplastic	Common	Never

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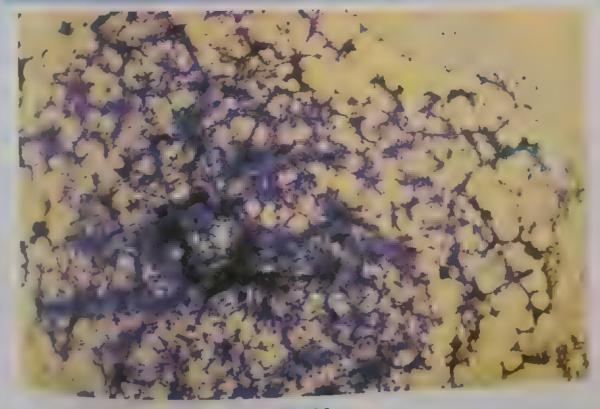
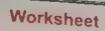


Fig. 16.2





APLASTIC ANEMIA 1 357

, Chapter of DQB to be done:

. EXTRA POINTS FROM DQB



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## AN OVERVIEW OF LYMPHOID NEOPLASMS

## CONCEPTS

- Lincept L/ L. An Overview of Lymphoid Neoplasma

PURROUN Concept 17.1 An Overview of Lymphoid Neoplasms

Concept 1. 1 All Concep

#### Time Needed

1º reading	60 mis	
2 <sup>nd</sup> reading	30 mm	

Non ancient chromosomal abnormalities, most commonly translocations, are present

Leckeria s used for neoplasms that present with widespread involvement of the pore mar on and (usually, but not always) the peripheral blood. Lymphoma is used for

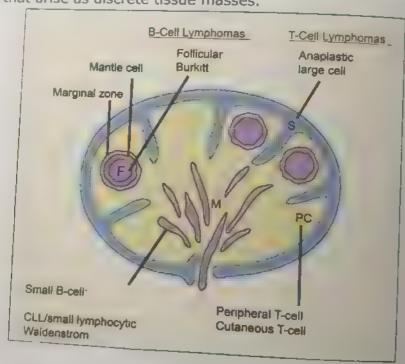


Fig. 17 1

Sites of origin of malignant lymphomas in a lymph node according to anatomic and functional compartments of the immune system. CLL, chronic lymphocytic leukemia; F, follicles with germinal centers; M, medullary cords; PC, paracortex, or interfollicular areas; S, sinuses.

# The Who Classification of the Lymphoid Neoplasms:

- The vast majority (85% to 90%) of lymphoid neoplasms are of B-cell origin, with most of the remainder being T-cell tumors; only rarely are tumors of NK cell origin
- Most lymphoid neoplasms resemble some recognizable stage of B- or T-cell



il dina Beritina

thronic lymphocytic leukemia/small lymphocytic lymphoma

Monoclonal B-cell lymphocytosis\*

B-cell prolymphocytic leukemia

Splenic marginal zone lymphoma

Hairy cell leukerma

Splenic B-cell lymphoma/leukemia, unclassifiable

Splenic diffuse red pulp small B-cell lymphoma

Harry cell leukemia-variant

Lymphoplasmacytic lymphoma

Waldenström macroglobulinemia

Monoclonal gammopathy of undetermined significance (MGUS), IgM\*

μ heavy-chain disease

y heavy-chain disease

a heavy-chain disease

Monoclonal gammopathy of undetermined significance (MGUS), IgG/A\*

Plasma cell myeloma

Solitary plasmacytoma of bone

Extraosseous plasmacytoma

Monoclonal immunoglobulin deposition diseases\*

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Nodal marginal zone lymphoma

Pediatric nodal marginal zone lymphoma

Follicular lymphoma

In situ follicular neoplasia\*

Duodenal-type follicular lymphoma\*

Pediatric-type follicular lymphoma\*

Large B cell lymphoma with IRF4 rearrangement\*

Primary cutaneous follicle center lymphoma

Mantle cell lymphoma

In situ mantle cell neoplasia\*

Diffuse large B-cell lymphoma (DLBCL), NOS

Germinal center B-cell type\*

Activated B-cell type\*

T-cell/histrocyte-rich large B-cell lymphoma

Primary DI BCL of the central nervous system (CNS)

Primary cutaneous DLBCL, leg type

EBV+ DLBCL, NOS\*

1.3\ mucocutaneous ulcer\*

Vi Re Lassociated with chronic inflammation

Lymphomatoid granulomatosis

2 - 4rv mediastinal (thymic) large B-cell lymphoma

lar avascular large B-cell lymphoma

VLK+ large B-cell lymphoma

Plasmablastic lymphoma

Prary effusion lymphoma

HHV8+ DLBCL, NOS\*

Burkitt lymphoma

Burkitt-like lymphoma with 11q aberration\*

It gh-grade B-cell lymphoma, with MYC and BCL2 and or BCL6 rearrangements\*

High-grade B-cell lymphoma, NOS\*

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgk.n

Mature T and NK neoplasms

I-cell prolymphocytic leukemia

I-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorder of NK cells

Aggressive NK-cell leukemia

Systemic EBV+ T-cell lymphoma of childhood\*

Hydroa vacciniforme-like lymphoproliferative disorder\*

Adult T-cell leukemia/lymphoma

Extranodal NK-/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Monomorphic epitheliotropic intestinal f cell lymphoma\*

Indolent T-cell I, it priopro, derative disorder of the GI tract\* il jesto ja na 1 cest cytophonia

some resucces pages that like I cell lymphonia

M. c. Lawrides

sala vidiolas

Primary cettacous (130 - 1 celi lyn.phoproliterative disorders

Printary Culaneous anaplastic large cell lymphoma



Primary cutaneous γδ T-cell lymphoma

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic I-cell lymphoma

Primary cutaneous acrai CD8+ T-cell lymphoma\*

primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder\*

Peripheral T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma

Follicular T-cell lymphoma\*

Nodal peripheral T-cell lymphoma with TFH phenotype\*

Anaplastic large-cell lymphoma, ALK+

Anaplastic large-cell lymphoma, ALK-\*

Breast implant-associated anaplastic large-cell lymphoma\*

Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma

Classical Hodgkin lymphoma

Nodular sclerosis classical Hodgkin lymphoma

Lymphocyte-rich classical Hodgkin lymphoma

Mixed cellularity classical Hodgkin lymphoma

Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)

Plasmacytic hyperplasia PTLD

Infectious mononucleosis PTLD

Florid foilicular hyperplasia PTLD\*

Polymorphic PTLD

Monomorphic PTLD (B- and T-/NK-cell types)

Classical Hodgkin lymphoma PTLD

Histocytic and dendritic cell neoplasms

Histocytic sarcoma

Langerhans cell histiocytosis

Langerhans cell sarcoma

Indeterminate dendritic cell tumor

Interdigitating dendritic cell sarcoma

Follicular dendritic cell sarcoma

Fibroblastic reticular cell tumor

Disseminated juvenile xanthogranuloma

Frdheim-Chester disease\*



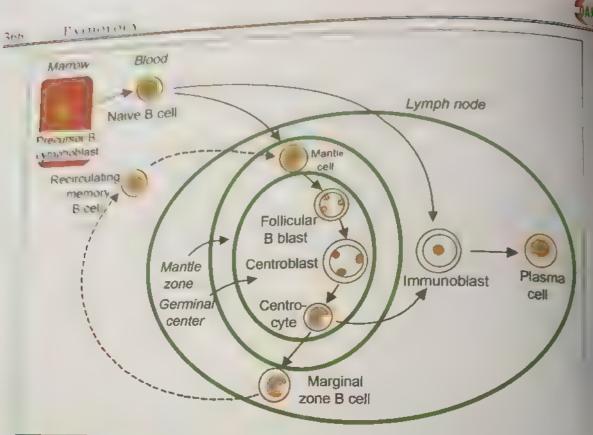
## me Immune Cell Antigens Detected By Monoclonal Antibodies:

lesignation	Normal Cellular D
Primarily T-	Cell Associated
w)	Thymocytes and Langerhans cells
CD3	Thymocytes, mature T cells
CD4	Helper T cells, subset of thymocytes
CD5	T cells and a small subset of B cells
CDN	Cytotoxic T cells, subset of thymocytes, and some NK cells
Primarily B-C	ell Associated
CD 3	Pre-B cells and germmal-center B cells; also called CALLA
	Pre-B cells and mature B cells but not plasma calls
( 55	Pre-B cells after CD19 and mature B cells but not plasma cells
	EBV receptor, mature B cells and follicular dendritic cells
223	Activated mature B cells
CD~9a	Marrow pre-B cells and mature B cells
Primarily Mono	tyte or Macrophage-Associated
( )) (	Granulocytes, monocytes and monocytes
	Immature and mature monocytes and granulocytes  Monocytes
7 ° ¢	Monocytes
	Granulocytes, Reed-Sternberg cells and variants
	Myeloid progenitors and monocytes
194	Mature myeloid cells
By MK-Cell	Associated
CD16	K cells and granulocytes
CD56	K cells and and
Primarily Stem Cel	A sells and a subset of T cells  and Progenitor Cell -Associated
- 4	Three as I
ACHIVATION MAI	Opotent hematopoietic stem cells and progenitor cells of many lineages
, A	the data progenitor cells of many lineages
Present On All Leuk	ocytes  (i. 1) cells, and monocytes, Reed Sternberg cells and variants  (ii. 1) cells, and monocytes, Reed Sternberg cells and variants
Au Au	A yes Reed Stemberg cells and variants
ALLA COLL	n. 18 K ytes; also known as look

All it is regites; also known as leukocyte common antigen (L(A)

for a state act and the length of the lenkemia antipen, (1) cluster designation, FBV. Epstem-Barr virus.

-	Pathologic	Features in the Differ	Victor Day	gross of	Sympositivities	TOTO IVEO	LASMS   36
Lymphoma	Growth Pattern	Cytology	Immuno	phenotype	man B-L-C		
Type	I attern	1	CD5	CD10	CD23	Surface Ig	Genetics
Fo Leular lymphoma	Nodular (follicular)	Lymphocytes with irregular cleaved nuclei (centrocytes) and admixed large cells (centroblasts)	-	+		Bright	t(14;18)(q32;   q21) m >85%
B-cell caron- ic viriphocyt- ic retikemia small lymphocytic lymphoma	Diffuse with proliferation centers	Small lymphocytes with round nuclei and scant cytoplasm	+			Weak IgM and IgD > IgG > IgA	Insomy 12 deletions of 13q, 6q, 11q and 17p; rearranged 14q 32
cymphop asmacytic 'ymphoma	Diffuse or interfollic- ular	Small lymphocytes, plasma cells, and plasmacytoid lymphocytes	-	-		Moderate IgM	Deletion 6q
Mantle cell lymphoma	Diffuse or vaguely nodular	Small lymphocytes with irregular nuclei, scant cytoplasm, and few admixed large cells	+	_ &		Moderate IgM and IgD; λ>κ	t(11;14) (q13; q32)
nodal narginal one B-cell ymphoma	Interfollicu- lar and peris- inusoidal	Small lymphocytes with round, folded nuclei and abundant cytoplasm plasma cells	-	The second second	T T T T T T T T T T T T T T T T T T T	Moderate IgM	None
plenic pargmal one B-cell mphoma	Nodular	Biphasic: inner core of small lymphocytes with irregular nuclei and scant cytoplasm; outer core of medium- size lymphocytes with round nuclei and abundant clear cytoplasm * plasma cells				IgM ± IgD	Deletion 7q
xtranodal arginal one B-cell mphoma mucosa- sociated mphoid sue	Diffuse	Small lymphocytes with round, folded nuclei and abundant cytoplasm ± plasma cells	-	-	-	IgM	Trisomy 3 or t(11;18) (q21;q21)



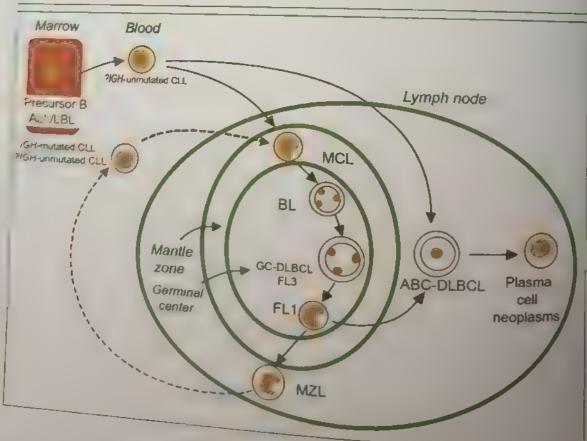


Fig. 17.2

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Syndrome	Altered Genes		Mechanism	Leukemia Type	
	Inheritance	Description			
Ataxia telangiectasia	R	ATM homozygotes	Genomic instability	T-cell lymphoma, T-cell ALL, T-cell	
		Dominant- negative missense mutations	Increased translocations in T cells formed at the time of V(D)J recombination	PLL, B-cell lymphoma	
Broom	R	BLM	Genomic instability	ALL, lymphoma	
Nijmegen breakage	R	NBS1	Genomic instability Altered telomere maintenance	Lymphoid tumors, especially B-cell lymphoma	
Li-Fraumení*	D	p53	Defect in tumor suppressor	CLL, ALL, Hodgkin and Burkitt lymphoma	
Common variable immunodeficiency	R and D	Defect in CD40 signaling	Failure of B-cell maturation	Burkitt, MALT, other B-cell lymphomas, Hodgkin lymphoma	
Severe combined immunodeficiency disease (SCID)	R	ADA	Defective T- + B-cell function	B cell lymphoma	
Wiskott-Aldrich	Х	WASP	Signaling and apoptosis	Hodgkin and non Hodgkin lymphoma	
X-linked immunodeficiency with normal or increased IgM	Х	CD40L	CD40 ligand defect on T cell	Hodgkin and non- Hodgkin lymphoma	
X-linked lymphoproliferative syndrome (XLP)	Х	SAP	Defect in immune signaling	EBV-related B cell lymphoma	
Autoimmune lymphoproliferative syndrome (ALPS)	D	APT (FAS)	Germ-line heterozygous FAS mutations; defective apoptosis	Lymphoma	

Human herpesvirus 8

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#### A sended with the Development of Lymphoid Malignancies Lymphoid Malignancy Infectious Agent Burkitt's lymphoma Epstein-Barr virus Post-organ transplant lymphoma Primary CNS diffuse large B cell lymphoma Hodgkin's disease Extranodal NK/T cell lymphoma, nasal type HTLV-I Adult T cell leukemia/lymphoma HIV Diffuse large B cell lymphoma Burkitt's lymphoma Hepatitis C virus Lymphoplasmacytic lymphoma Helicobacter pylori Gastric MALT lymphoma

Primary effusion lymphoma

Multicentric Castleman's disease

Agent Infections And A	ssocia, ions With Lympnoma
Hepatitis C virus	Lymphoma Type(s)
Campylobacter jejuni	Splenic marginal zone lymphoma; other B-cell lymphomas
Borrelia burgdorferi	Immunoproliferative small intestinal disease
Chlamydia psittaci	Primary cutaneous B-cell lymphoma
aExtranodal marginal zone lymphoma, MALT-ty	



11

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### The Ann Arbor Staging System for Hodgkin's Disease

	2 4.00
Stage	Definition
JEDD.	

Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)

Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides constitute stage II disease)

Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm

Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes

Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III1

Involvement of extranodal site(s) beyond that designated as "E"

More than one extranodal deposit at any location

Any involvement of liver or bone marrow

#### A No symptoms

I nexplained weight loss of >10% of the body weight during the 6 months before staging investigation

Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month

Recurrent drenching night sweats during the previous month

Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

#### International Prognostic Index for NHL

Five clinical risk factors:

Age 60 years

Serum lactate dehydrogenase levels elevated

Performance status 2 (ECOG) or 70 (Karnofsky)

Ann Arbor stage III or IV

\*! site of extranodal involvement

Patients are assigned a number for each risk factor they have

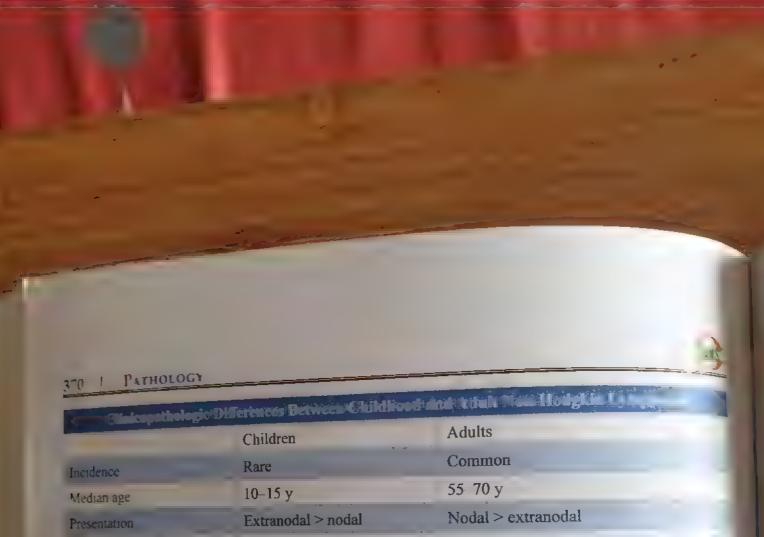
Patients are grouped differently based upon the type of lymphoma

For diffuse large B cell lymphoma:

0. 1 factor ≈ low risk:	35% of cases; 5-year survival, /3%
2 factors - low-intermediate risk:	27% of cases 5-year survivat, 51%
3 factors = high-intermediate risk:	22% of cases: 5-year survival, 43%
4, 5 factors = high risk:	16% of cases; 5-year survival, 26%

#### For diffuse large B cell lymphoma treated with R-CHOP:

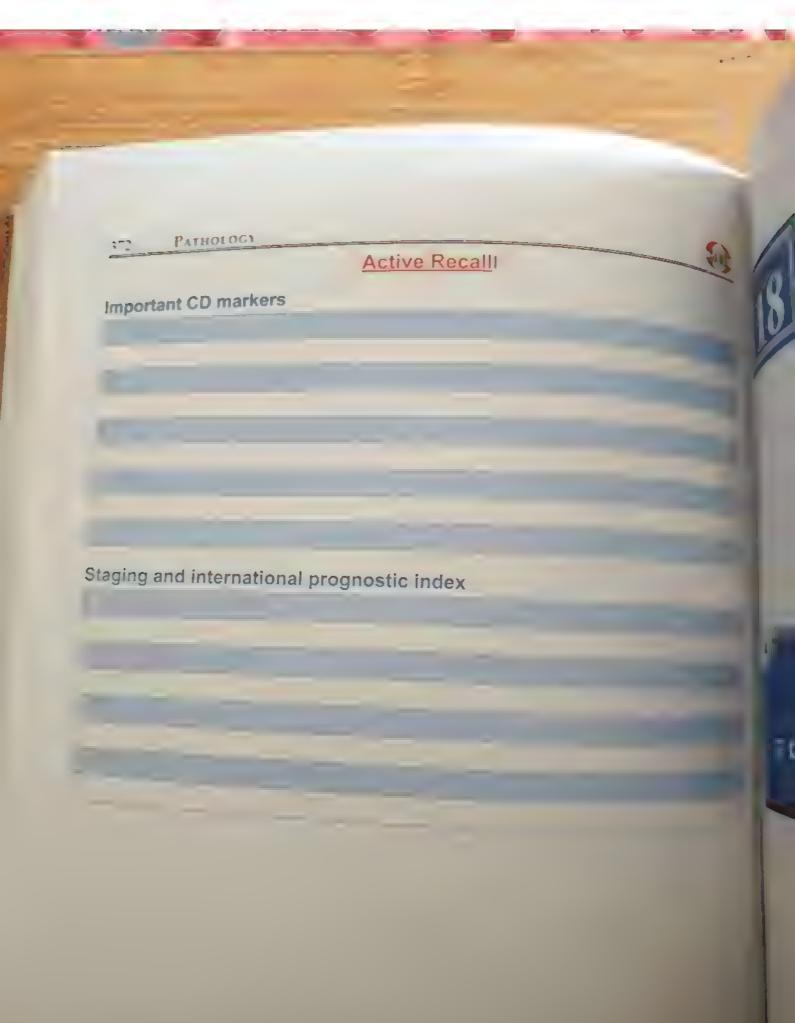
O factor = very good:	10% of cases: 5-year survival, 94%
1,2 factors - good:	45% of cases, 5-year survival, 79%
3.4.5 factors = poor:	45% of cases; 5-year survival, 55%



(in the state of the last of t	Herences Between Chinanous	The state of the s
	Children	Adults
Incidence	Rare	Соттоп
Median age	10–15 y	55 70 y
Presentation	Extranodal > nodal	Nodal > extranodal
Most common histologic diagnoses	B cell: Burkitt; diffuse large cell T cell: Lymphoblastic; ALK+ anaplastic large cell	B cell: Diffuse large cell (DLBCL). state cleaved (follicular center) cell  T cell: Peripheral T-cell, unspecified.  anaplastic large cell; angioimmunob.
Immunophenotype	50–70% B cell	85-90% B cell (United States, Europ 50-70% T cell (Asia)
Paraprotein	None	Rare (<5%)
Chnical course	Aggressive	Variable-often indolent
Curability	70-90%	<30%, except 40–70% in aggressive subtypes, particularly DLBCL

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### LYMPHOID NEOPLASMS

## CONCEPTS

Concept 18.1: Lymphoid Neoplasms



#### PATHOLOGY

374 Concept 18.1: Lymphoid Neoplasms

Concept 18.1: Lymphores of lymphomas (genetics, C/F, markers, Prognosis, Treatment

#### Time Needed

t <sup>a</sup> reading		3 hours
2 <sup>nd</sup> reading	1	90 min

- Within the large group of lymphomas, Hodgkin lymphoma is segregated from all other forms, which constitute the non-Hodgkin lymphomas (NHLs).
- The other important group of lymphoid tumors is the plasma cell neoplasms. These most often arise in the bone marrow and only infrequently involve lymph nodes or the peripheral blood.
- · The clinical presentation of the various lymphoid neoplasms is most often determined by the anatomic distribution of disease.
- Two thirds of NHLs and virtually all Hodgkin lymphomas present as enlarged nontender lymph nodes (often >2 cm).
- The remaining one third of NHLs present with symptoms related to the involvement of extranodal sites (e.g., skin, stomach, or brain).
- The lymphocytic leukemias most often come to attention because of signs and symptoms related to the suppression of normal hematopoiesis by tumor cells in the
- Finally, the most common plasma cell neoplasm, multiple myeloma, causes bony destruction of the skeleton and often presents with pain due to pathologic fractures.
- However, it should also be kept in mind that certain lymphoid tumors cause symptoms through the secretion of circulating factors

RISK Factors

Age -66 years

Serum lactic denydrogenase greater than twice normal

Port rimar de status >2

Stage III or IV

Extranodal involvement at 11 site



School Service

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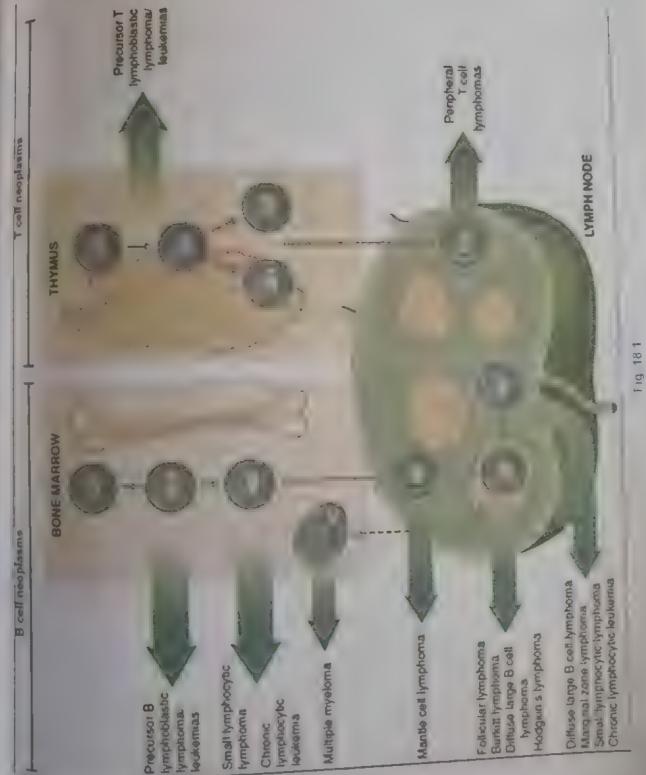
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Chronic



Summary of Major Types of Lymphoid Leukemias and Non-Hodgkin Lymphomas:

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and the second second		o landario de la constanti de	
B-ceil acute lymphobit s' coukemia/lymphoma	Bone marrow precursor B cell	Diverse chromosomal translocations; t(12;21) involving CBFa and ETV6 present in 25%	Predominantly children; symptoms relating to marrow replacement and pancytopenia; aggressive
I-cell acute lymphoblastic leukemia/lymphoma	Precursor 1 cell (often of thymic origin)	Diverse chromosomal translocations, NOTCH1 mutations (50% to 70%)	Predominantly adolescent males; thymic masses and variable bone marrow involvement; aggressive
Neoplasms of Mature	e B Cells		A 3-1
Burkitt lymphoma	Germinal- center B cell	Translocations involving c-MYC and lg loci, usually t(8;14); subset EBV-associated	Adolescents or young adults with extranodal masses; uncommonly presents as "leukemia"; aggressive
Diffuse large B-cell lymphoma	Germinal- center or post germinal-center B cell	Diverse chromosomal rearrangements, most often of BCL6 (30%), BCL2 (10%), or c-MYC (5%)	All ages, but most common in adults; often appears as a rapidly growing mass; 30% extranodal; aggressive
Extranodal marginal zone lymphoma	( Memory B cell	t(11;18), t(1;14), and t(14;18) creating MALT1-IAP2, BCL10- IgH, and MALT1- IgH fusion genes, respectively	Arises at extranodal sites in adults with chronic inflammatory diseases; may remain localized; indolent
Follicular lymphoma	Germinal- center B cell	t(14:18) creating BCL2- IgH fusion gene	Older adults with generalized lymphadenopathy and marrow involvement; indolent
Hairy cell leukemia		No specific chromosomal abnormality	Older males with pancytopenia and splenomegaly; indolent
Mantle cell lymphoma	Naive B cell	t(11;14) creating CyclmD1-IgH fusion gene	Older males with disseminated disease; moderately aggressive
Multiple myeloma/ solitary plasmacytoma	Post-germinal- center bone	Diverse rearrangements involving IgH; 13q deletions	Myeloma, older adults with lync bone lesions, pathologic fractures, hypercalcemia, and renal failure, moderately aggressive
			Plasmacytoma, isolated plasma cell masses in bone or soft fissae.

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Small lymp	i i i i i i
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Lagarit	re leukemia
time nocy i	ID to
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Naive B cell or Trisomy 12, deletions of memory B cell 11q, 13q, and 17p

Older adults with bone marrow, lymph node, spleen, and liver disease; autoimmune hemolysis and thrombocytopenia in a minority; indolent

### Neoplasms of Mature T Cells or Nk Cells

Adult T-cell	leukemia/
ymphoma	

Helper T cell

HTLV-1 provirus present in tumor cells

Adults with cutaneous lesions, marrow involvement, and hypercalcemia; occurs mainly in Japan, West Africa, and the Caribbean; aggressive

Pempheral T-cell	
lymphoma, unspecific	d
lymphoma, unspecific	II.
il	

Helper or cytotoxic T cell No specific chromosomal abnormality.

Mainly older adults; usually presents with lymphadenopathy; aggressive

Anaplastic large-cell , mp., 1110

Cytotoxic T cell

Rearrangements of ALK

Children and young adults, usually with lymph node and softtissue disease; aggressive

#### Extranodal NK/T-cell lymphoma

NK-cell (common) or cytotoxic T cell (rare)

EBV-associated; no specific chromosomal abnormality

Adults with destructive extranodal masses, most commonly sinonasal; aggressive

Mycosis fungoides/ Sézary syndrome

Helper T cell

No specific chromosomal abnormality

Adult patients with cutaneous patches, plaques, nodules, or generalized erythema; indolent

Large granular ymphocytic leukemia

Two types: cytotoxic T cell and NK cell

No specific chromosomal abnormality

Adult patients with splenomegaly, neutropenia, and anemia, sometimes, accompanied by autoimmune disease

#### Acute Lymphoblastic Leukemia:

Acute Lymphobiastic	Leukenna.	ute Lamphoid Leul	centia (ALL)
Immunologic Subtype	% of Cases	FAB Subtype	Cytogenetic Abnormalities
Pre-B ALL	75	L1, L2	π(9,22), π(4,11), π(1,19)
T cell ALL	20	L1, L2	14q11 or 7q34 1(8;14), t(8;22), t(2;8)
B cell ALL	5	L3	1(0,17), 40,22,1-(-1-7

#### ALL is the most common cancer of children

Approximately half of patients present with fever, which often is induced by pyrogenic cytokines (e.g., interleukin-1, interleukin-6, and tumor necrosis factor) released from

In these patients, fever resolves within 72 hours after the start of antileukemic leukemic cells

Among the frequently evident findings are pallor, petechiae, and ecchymosis in the skin and mucous membranes, and bone tenderness as a result of leukemic infiltration or hemorrhage that stretches the periosteum.



spleen, and lymph nodes are the most common sites of extramedullary ne spleen, and lymph nodes are the more pronounced in children than

1 leukemic presentations, the marrow is hypercellular and packed with lymphoblasts,

which replace the normal marrow elements. Which replace the normal marrow electron to 70% of T-ALLs, which are also more like y Mediastinal thymic masses occur in 50% to 70% of T-ALLs, which are also more like y

हिन्द कर्ति with lymphadenopathy and splenomegaly. In both B- and I-ALL, the tumor cells have scant basophilic cytoplasm and nucer

smen at arger than those of small lymphocytes.

at anger than those of striction of pre-B cell development. The lymphoblasts the pan B-ce | marker CD19 and the transcription factor PAX5, as we The very immature B-ALLs, CD10 is negative. Alternatively, more mature Reports ALLs express CD10, CD19, CD20, and cytoplasmic IgM heavy chain (

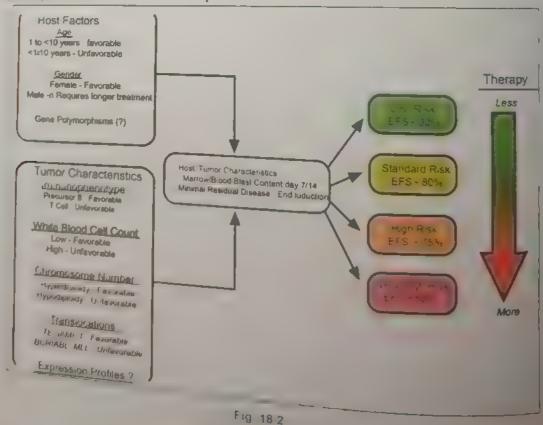
• Start TALLS are arrested at various stages of pre-T cell development. In most cases the Lei's are positive for CD1, CD2, CD5, and CD7. The more immature tumors are usually negative for surface CD3, CD4, and CD8, whereas "late" pre-T cell tumors ore positive for these markers.

· Approximately 90% of ALLs have numerical or structural chromosomal changes Most common is hyperploidy (>50 chromosomes).

The total WBC count at the time of diagnosis is the single most powerful clinical determinant of remission induction, remission duration, and long-term survival for a age groups.

Examination of the cerebrospinal fluid (CSF) is an essential diagnostic procedure.

Tracitionally, CNS leukemia is defined by the presence of at least 5 leukocytes per recorder of CSF (with leukemic blast cells apparent in a cytocentrifuged sample) or ty the presence of cranial nerve palsies.





## S: event free survival:

S: event not a vaniation in vaniation in vania	S. with Cent Lympheblas II. Limited Street, 1985
tent Features	Pro mostic Factor
ge (y)	I avorabie
0	Unfavorable
hite blood cell count ×(106/ml)	
	Favorable
0.000	Unfavorable
munophenotype	
,   }_[	Favorable
e B-cell ALL; early T-cell ALL	Unfavorable
	Ferrando
o_mormality; t(10;14)(q24;q11)	Favorable
water in perdiploid	Intermediate
22 . 4.11 t(1;19), hypodiploid, -7, +8	Unfavorable
esponse to therapy	
The cite remission within 4 wk	Favorable
es stem minima, residual disease	Unfavorable

And Constitution	interpretation of	
icern nants	Favorable	Unfavorable
W blood cell counts	<10 × 109/L	>200 × 109/L
114	3 7 y	<1 y. >10 y
Gender	Female	Male
. L. city	White	Black
Node, liver, spleen enlargement	Absent	Massive
Test cular enlargement	Absent	Present
Central nervous system leukenna	Absent	Overt (blasts + pleocytosts)
FAB morphologic features	Ll	1.2
P oldy	Hyperdiploidy	Hypodiploidy 545
We genetic markers	Trisomies 4, 10, and/or 17	t(9,22) (BCR-ABL)
regenetic markers	t(12;21) (TEL-AML1)	t(4;11) (MLL-AF4)
h (		>28 d
m. to remission	<14 d	≥10-3
M residual disease	<10-4	



#### PATHOLOGY 380

Treatment and Supportive Care:

Treatment and Supportive Care.

• Hyperuricemia and hyperphosphatemia with secondary hypocalcemia are frequently.

• Hyperuricemia and hyperphosphatemia with secondary hypocalcemia are frequently. Hyperuricemia and hyperphosphatering the hyperuricemia and hyperu encountered at diagnosis, even before B-cell leukemia with high feukemic cell burden, with B-cell or T-cell ALL or precursor B-cell leukemia with high feukemic cell burden. with B-cell or 1-cell ALL of presents should be given intravenous fluids; allopurinol or rasburicase (recombinant urate

Patients should be given intraverious trade, and a phosphate binder, such as aluminum hydroxide, oxidase) to treat hyperuricemia; and a phosphate binder, such as aluminum hydroxide, oxidase) to treat hyperuncernia, and o provide, calcium carbonate (if the serum calcium concentration is low), lanthanum carbonate, or sevelamer to treat nyperphosphatemia.

• The most effective contemporary treatment regimens for B-cell ALL are drug The most effective contemporary to the most effective contemporary to the drug combinations that include cyclophosphamide given over a relatively short time (3-6) months).

 Systemic treatment including high-dose methotrexate, intensive asparaginase, and dexamethasone, as well as optimal intrathecal therapy, is important to control CNS leukemia. Tr.ple intrathecal therapy with methotrexate, cytarabine, and hydrocortisone is more effective than intrathecal methotrexate in preventing CNS relapse.

 The induction regimen typically includes a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and L-asparaginase for children or an anthracycline for adults.

· Consolidation phase. More commonly used regimens for childhood ALL include highdose methotrexate with or without mercaptopurine, high-dose L-asparaginase given for an extended period, or a combination of dexamethasone, vincristine, L-asparaginase,

and doxorub	picin, followed by thioguanine, cytarabine,	and cyclophosphamide.
C	Side Effects Associated with Authenkemi	
Treatment	Acute Complications	Delayed Complications
Prednisone (or prednisolone)	Hyperglycemia hypertension, changes in mood or behavior, acne, increased appetite, weight gain, peptic ulcer, hepatomegaly, myopathy	As no seeds
Dexamethasone	Same as prednisone, except for increased changes in mood or behavior and myopathy but less salt retention	Same as prednisone
Vincristine	Penpheral neuropathy, constipation, chemical cellulitis, seizures, hair loss	None
Daunorubicin, .Jarubicin doxorubicin, or epirubicin	Nausea and vomiting, hair loss, mucositis, marrow suppression, chemical cellulitis, increased skin pigmentation	Cardiomyopathy (with high cumulative dose)
L-Asparaginase  Mercaptopurine	Nausea and vomiting, allergic reactions (manifested as rashes, bronchospasm, severe pain at inframuscular injection site), thrombosis, encephalogost, liver dysfunction.	None
	Nausea and vomiting, mucositis, marrow suppression, solar dermatitis, liver persons lacking thiopurine methystransferase	Osteoporosis (long-term use), acute myeloid leukemia in persons with thiopurine methyltransferase deficiency

	L	YMPHOID NEOPLASMS   381
Methotrexate	Nausea and vomiting, liver dysfunction, I marrow suppression, mucositis (resulting from high-dose treatment), solar dermatitis	eukoencephalopathy, osteopenia resulting from long-term use)
Etoposide, teniposide	Nausea and vomiting, hair loss, mucositis, marrow suppression, allergic reactions (bronchospasm, urticaria, angioedema, hypotension)	
Cytar sping	Nausea and vomiting, fever, skin rashes, mucositis, marrow suppression, liver dysfunction, conjunctivitis (resulting from high-dose treatment)	cumulative dose)
Cyclophosphamide	Nausea and vomiting, hemorrhagic cystitis, marrow suppression, syndrome of inappropriate secretion of antidiuretic hormone, hair loss	Bladder cancer or acute myeloid leukemia (rare), decreased fertility (with high cumulative dose)
Ruay mah	Infusion reactions, mucocutaneous reactions, cardiac arrhythmias, lymphopenia	Reaction of virus infections progressive multifoca leukoencephalopathy from JO virus infection
Intrainecal	Headache, fever, seizure, marrow suppression, mucositis (in patients with renal dysfunction)	(MICH DISH
Brain irradiation	Hair loss, postirradiation somnolence syndrome (6-10 weeks after treatment)	Seizure, mineralizing micro angiopathy, growth hormon deficiency, thyroid dysfunction obesity, osteopenia, brain tumor basal cell carcinoma, parotid glav carcinoma, hair loss, catara (rare), dental abnormalities

#### Burkitt's Lymphoma:

It was the first tumor to be etiologically associated with

- 1. a virus, specifically Epstein-Barr virus,
- 2. a specific chromosomal translocation involving chromosome 8, and
- 3. one of the first cancers shown to be curable by chemotherapy alone.
- It presents in three clinically distinct forms: endemic, sporadic, and immunodeficiency
- The unifying feature of all three types of BL is activation of the MYC gene via immunoglobulin (Ig) translocation leading to high levels of MYC protein, which activates transcription of a plethora of genes involved in cell growth.
- The endemic (African) form often presents as a jaw or facial bone tumor. It may spread to extranodal sites, especially to the marrow and meninges. Almost all cases
- The nonendemic or American form presents as an abdominal mass in approximately 65 percent of cases, often with ascites. Extranodal sites, such as the kidneys, gonads,



breast, marrow, and central nervous system (CNS) may be involved. Involvement of breast, marrow, and central nervous system in the nonendemic form. Patients of the marrow and CNS is much more common in the nonendemic form. Patients with the marrow and CNS is much more with malignant cells often are referent marrow involvement with malignant cells often are referenced. the marrow and CNS is much more common with malignant cells often are referred to more than 25 percent marrow involvement. In addition, in contrast to the endemice to more than 25 percent marrow involvement addition, in contrast to the endemic form, as having acute Burkitt cell leukemia. In addition, in contrast to the endemic form, only 15 percent of the nonendemic cases are EBV positive. only 15 percent of the nonendermonal and are associated and are associated and are associated.

with EBV in 30 percent of the cases. • The tumor exhibits a high mitotic index and contains numerous apoptotic

The tumor exhibits a night interest are phagocytosed by interspersed benign macrophages.
 These phagocytes have abundant clear cytoplasm, creating a characteristic "starry

sky" pattern. • When the bone marrow is involved, aspirates reveal tumor cells with slightly clumped

When the bone marrow is involved, as involve ciear cytoplasmic vacuoles.



• Ali cases of BL have a translocation between the long arm of chromosome 8, the ste of the MYC protooncogene (8q24), and one of three translocation partners: the <sup>19</sup> heavy-chain region on chromosome 14; the κ light-chain locus on chromosome 2; of

- A key feature of BL is the relative simplicity of their karyotype: In a good proportion A key reaction a good proportion of cases, the MYC translocation is the sole abnormality. This distinguishes it from d fruse large B-cell lymphoma
- These are tumors of mature B cells that express surface IgM, CD19, CD20, CD10, These and a phenotype consistent with a germinal center B-cell origin. Unlike other tumors of germinal center origin, Burkitt lymphoma almost always fails to express the ant apoptotic protein BCL2.
- The regimens employ multiple non-cross-resistant drugs used over a short period. These drugs include high-dose cyclophosphamide, methotrexate, vincristine, prednisone, high-dose methotrexate, high-dose cytarabine, etoposide, and sometimes
- . CNS prophylaxis therapy, either intrathecal or systemic, is given in almost all patients with BL. Radiation therapy does not play a role in the treatment of BL.

#### Diffuse Large B Cell Lymphoma:

- . Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL (\*)
- . Inc dence increases with age; the median age at presentation is in the seventh decade.
- . The disease typically presents as a nodal or extranodal mass with rapid tumor growth associated with systemic symptoms.
- Pat ents with DLBCL typically present with a rapidly enlarging, symptomatic, lymphatic masses. The typical presentation is of a rapidly enlarging lymph node in the neck or an abdominal mass.
- Extranoda disease occurs in approximately 40 percent of patients, most commonly nvolving the gastrointestinal tract (\*). Other sites that may be affected include the testis, bone, thyroid, salivary glands, skin, liver, breast, nasal cavity, paranasal sinuses, and central nervous system (CNS).
- DLBCL can be highly invasive, with local compression of vessels (e.g., superior vena cava syndrome) or airways (e.g., tracheobronchial compression) requiring urgent treatment.
- These mature B-cell tumors express CD19 and CD20 and show variable expression of germinal center B-cell markers such as CD10 and BCL6. Most have surface Iq.
- One frequent pathogenic event is dysregulation of BCL6, a DNA-binding zinc-finger transcriptional repressor that is required for the formation of normal germinal centers.
- About 30% of DLBCLs contain various translocations that have in common a breakpoint in BCL6 at chromosome 3q27.

## Several other subtypes of DLBCL are sufficiently distinctive to merit brief

- Immunodefic ency-associated large B-cell lymphoma occurs in the setting of severe T-cell immunodeficiency (e.g., advanced HIV infection and allogeneic bone marrow transplantation). The neoplastic B cells are usually infected with EBV, which plays a critical pathogenic role. Restoration of T-cell immunity may lead to regression of these proliferations.
- Primary effusion lymphoma presents as a malignant pleural or ascitic effusion, mostly n patients with advanced HIV infection or the elderly. The tumor cells are often



The first of the second typically fail to express surface B- or T cell markers, but the in appropriate and typically fail to express surface B- or T cell markers, but the interest of the surface and typically fail to express surface B- or T cell markers, but the interest of the surface and typically fail to express surface B- or T cell markers, but the surface B- or T cell markers are surface B- or T cell markers, but the surface B- or T cell markers are surface B- or T cell markers. have clonal IgH gene rearrangements. In all cases the tumor cells are infected with kSHV/HHV-8, which appears to have a causal role onmon features are a relatively large cell size (usually four to five times the

ameter of a small lymphocyte) and a diffuse pattern of growth. ameter of a small lymphocyte, and doxorubicin, vincristine, prednisone and thent: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone R CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Mara hal Zone Lymphomas: Variational Zone Lymphoma encompasses a heterogeneous group of B-ce with n lymph nodes, spleen, or extranodal tissues.

11 - 12 Big Se Michael Symphomas comprise three distinct clinicopathologic entries who presentations, namely, the extranodal marginal zone lymphomas asc presentations, riality, see (MALT) lymphoma, the nodal marginal zone and the splenic marginal zone lymphoma. The extranodal type is the most and the spicific triangular for approximately 7.5 percent of all cases of non-Hodgkin lymphoma he extranodal tumors were initially recognized at mucosal sites and are often referred to as mucosa-associated lymphoid tumors (or "maltomas").

in most cases, the tumor cells show evidence of somatic hypermutation and are dered to be of memory B-cell origin.

an all marginal zone lymphomas share certain features, those occurring at intranodal sites deserve special attention because of their unusual pathogenesis and three exceptional characteristics.

- · They often arise within tissues involved by chronic inflammatory disorders of autoimmune or infectious etiology; examples include the salivary gland in Sjogren disease, the thyroid gand in Hashimoto thyroiditis, and the stomach in Helicobacter gastritis.
- They remain localized for prolonged periods, spreading systemically only late in their course.
- · They may regress if the inciting agent (e.g., Helicobacter pylori) is eradicated.
- · These characteristics suggest that extranodal marginal zone lymphomas arising in chronically inflamed tissues lie on a continuum between reactive lymphoid hyperplasia and full-blown lymphoma.
- Trie disease begins as a polyclonal immune reaction.
- · Art the acquisition of still-unknown initiating mutations, a B-cell clone emerges that July depends on antigen-stimulated T-helper cells for signals that drive growth and sory val. At this stage, withdrawal of the responsible antigen causes tumor involution.
- A control y relevant example is found in gastric "maltoma," in which antibiotic therapy checked against H. pylori often leads to tumor regression.
- and survival appears turnors may acquire additional mutations that render their growth and survival antigen-independent, such as the (11;18), (14;18), or (1;14) chromosomal translocations, which are related to the survival antigen-independent, such as the (11;18), (14;18), or (1;14) chromosomal translocations.
- All of three transfords which are relatively specific for extranodal marginal zone lymphomas. • All of these translocations up regulate the expression and function of BCL10 or MALT1, protein components of a contest the protein components of a signaling complex that activates NF-kB and promotes the



Follicular Lymphoma: Follicular Eyes from germinal center B cells and is strongly associated the tumor likely arises from germinal center B cells and is strongly associated The tumor mosomal translocations involving BCL2. with cline.

with FL usually present with painless diffuse lymphadenopathy.

Patients the cytogenetic finding detected in FL is the t (14;18) (q32; q21) trans ocation that juxtaposes the **BCL**-2 gene on band q21 of chromosome 18 trans ocation.

With the immunoglobulin (Ig) heavy-chain gene on band 32 of chromosome 14.

Histologic transformation occurs in 30% to 50% of follicular lymphomas, most commonly to diffuse large B-cell lymphoma.

. Two principal cell types are present in varying proportions:

, small cells with irregular or cleaved nuclear contours and scant cytoplasm, referred to as centrocytes (small cleaved cells); and larger cells with open nuclear chromatin, several nucleoli, and modest amounts of cytoplasm, referred to as centroblasts.

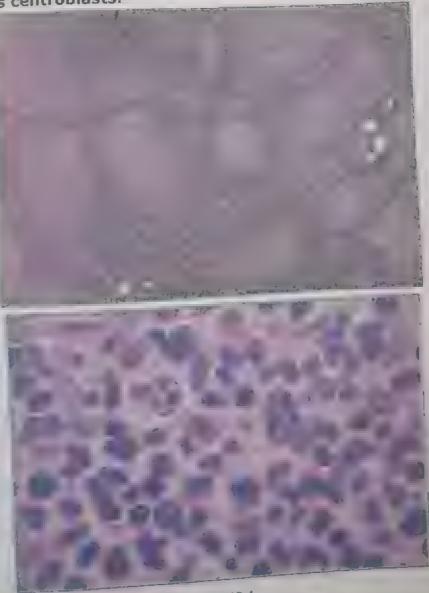


Fig. 18.4



F Jular lymphoma (lymphoma ells are present throughout lymph node. B, At high magnification, small lymphoid cells with condensed throughout lymph node, a, Acting in independent outlines (centrocytes) are mixed with a stin and irregular or cleaved nuclear outlines (centrocytes) are mixed with a population of larger cells with nucleoli (centroblasts).

## Harry Cell Leukemia/Leukemic Reticuloendotheliosis:

• It is predominantly a disease of middle-aged white males, with a median age of 55

- and a male-to-female ratio of 5:1. and a male-to-lettiale factory and a male-to-lettiale factory cells on a Wright-stained periphera
- www.mear is the single most important diagnostic finding. . See motionuclear with relatively abundant cytoplasm and a cell diameter in
- The Asm is pale blue-gray and agranular with a variable number of elongated = ry) projections.
- The nuclei are round, oval, reniform, or dumbbell-shaped with a nuclear chromating tatie in that is homogeneous and less clumped and lighter staining than that of normal Totale ymphocytes and those seen in classic CLL and prolymphocytic leukemia
- A prominent nucleolus is rarely seen.
- The marrow is involved by a diffuse interstitial infiltrate of cells with oblong or reniform nuclei, condensed chromatin, and pale cytoplasm.
- · Because these cells are enmeshed in an extracellular matrix composed of reticuin fibrils, they usually cannot be aspirated (a clinical difficulty referred to as a "dry tap" and are only seen in marrow biopsies.
- The spleen is almost always involved in HCL, and the pattern of hairy cell involvement, as with that in the bone marrow, is nearly pathognomonic for HCL.
- The infiltrates are confined to the red pulp, and, unlike other lymphoproliferative a corders, the white pulp is not expanded and is actually atrophic.
- Harry cell leukemias typically express the pan B-cell markers CD19 and CD20, surface in Josephy IgG), and certain relatively distinctive markers, such as CD11c, CD25. and CD103 Analysis of Ig gene sequences has revealed a high incidence of somatic Assert station, suggesting a post-germinal center memory B-cell origin.
- resonance 5 is involved in clonal aberrations in approximately 40 percent of pa with HCL, most commonly as trisomy 5 or as pericentric inversions and

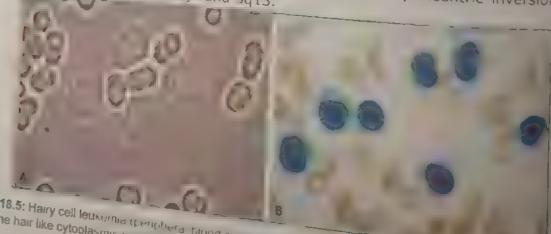


Fig. 18.5: Harry cell leuxernia (peripheral blood sinear.) A Phase-contrast microscopy shows tumor cells with fine hair like cytoplasmic projections. But stained smears these cens have round of folded nuclei and



## Mantle Cell Lymphoma:

It usually presents in the fifth to sixth decades of life and shows a male predominance.

Mantle cell lymphoma (MCL) is a lymphoma subtype that usually is characterized by cens carrying an immunophenotype similar to lymphocytes in the mantie zone of by terms and the cytogenetic abnormality in the mantie zone of normal germinal follicles, secretory immunoglobulin (sIg) M+, sIgD+, CD5+, CD20+, CD10-, CD43+, and the cytogenetic abnormality t(11;14) (q13;q32) in the tumor cells, resulting in the overexpression of cyclin D1.

MCL is still considered incurable. Because of the presence of advanced disease at presentation, most patients require systemic therapy. Current strategies involve intensification of therapy with or without consolidation with stem cell transplantation

(SCT).

9

### NOTE: Differential diagnosis- SLL/CLL AND FOLLICULAR LYMPHOMA.

The mmunophenotype of MCL has some similarities to that of chronic lymphocytic leukemia CLL or small lymphocytic lymphoma (SLL) in that the lymphoma cells express surface IgM and IgD and the B-cell -associated antigens CD19 and CD20, and have aberrant expression of the T-cell antigen CD5.

In contrast to CLL or SLL, MCL cells are positive for FMC7 and typically do not express CD23.

ake for icular lymphoma, MCL is positive for CD20 and BCL-2, but in contrast to follicular lymphoma, MCL is negative for CD10 and BCL-5.

This finding occurs because most cases do not originate in the germinal center but rather arise from naïve cells in the mantle zone of the follicle.

More importantly, almost all cases of MCL overexpress cyclin D1, and no other lymphoma shows overexpression of cyclin D1.

#### Plasma Cell Neoplasms:

Pasma cell neoplasms (PCNs) are monoclonal expansions of a single B lymphocyte characterized by plasma cell morphology and monoclonal immunoglobulin gene rearrangement. The vast majority of PCNs produce monoclonal immunoglobulin or immuno-Olobulin fragments

obulin fragments.		and the second second section of the second second	to the state of th
Some	Biologic		Immunodeficiency
	Myeloma	Monoclonal Gammopathy	
(	Large	Medium	Small
mmarozlobulin production	>30 g L	<30 g L	<3 g L
Tare course	Progressive	Persistent	Transient
Abnormal immunoglobulin structure	Frequent	Rare	Never
Bane destruction	Frequent	Never	Never
M use models			_
Transformed clone		+	
[ransp.antable generations	<4	_	
Action imous growth	+	+?	-
attal.ty	7		



Terms used to describe the abnormal Igs include monoclonal gammopathy, Terms used to describe the abiliornia. The following clinicopathologic entities are dysproteinemia, and paraproteinemia. The following clinicopathologic entities are

associated with monoclonal gammopathies. associated with monocional goldino, and myeloma), the most important monocional Multiple myeloma (plasma cell myeloma) masses scattered throughout the standard monocional masses scattered throughout the standard monocional masses scattered throughout the standard monocional masses as the most important monocional masses are monocional masses as the most important monocional masses are monocional masses as the most important monocional masses are monocional masses as the most important monocional masses are monocional masses and masses are monocional masses and masses are monocional masses and monocional masses are monocional masses and masses are monocional masses are monocional masses and masses are monocional masses and masses are monocional masses are monocional masses and masses are monocional ma

- Multiple myeloma (plasma tell myeloma) masses scattered throughout the skeleta gammopathy, usually presents as tumorous masses scattered throughout the skeleta gammopathy, usually presents as a system Soutary myeloma (plasmacytoma) is an infrequent variant that presents as a system Solitary myeloma (plasma Smoldering myeloma refers to another uncommon single mass in bone or soft tissue. Smoldering myeloma refers to another uncommon variant defined by a lack of symptoms and a high plasma M component.
- Waldenström macroglobulinemia is a syndrome in which high levels of IgM lead to Waldenstrom macroglobuline in older adults, most commonly in association with lymphoplasmacytic lymphoma.
- Heavy-chain disease is a rare monoclonal gammopathy that is seen in association with a diverse group of disorders, including lymphoplasmacytic lymphoma and an unusual small bower marginal zone lymphoma that occurs in malnourished populations (socalled Mediterranean lymphoma). The common feature is the synthesis and secretion of free heavy-chain fragments.
- Primary or immunocyte-associated amyloidosis results from a monoclonal proliferation. of plasma cells secreting light chains (usually of y isotype) that are deposited as amyloid. Some patients have overt multiple myeloma, but others have only a minor clonal population of plasma cells in the marrow.
- Monocional gammopathy of undetermined significance (MGUS) is applied to patients without signs or symptoms who have small to moderately large M components in their blood. MGUS is very common in the elderly and has a low but constant rate of transformation to symptomatic monoclonal gammopathies, most often multiple myeloma.

#### PCM:

Clonal bone marrow plasma cell percentage ≥ 10% or biopsy-proven plasmacytoma and - 1 of the following myeloma-defining events:

## End-organ damage attributable to the plasma cell proliferative disorder:

- Hypercaicaemia, serum caicium > 0.25 mmol.L (>1mg / DI) higher than the upper limit of Renal insufficiency:
- Creatinine clearance < 40 MI/minute or serum creatinine > 177 umol/L (>2 mg/DI).
- Anaemia, a haemogrobin value of >20 g/L below the lower limit of normal or a haemogrobin
- Bone esions > 1 osteolytic les on on skeletal radiography, CT, or PET/CT. - of the following biomarkers of malignancy:
- Clonal bone marrow plasma ceil percentage ≥ 60%.
- An involved-to-univolved serum free light chain ratio ≥ 100.

### Smouldering (asymptomatic) PCM. Both criteria must be met:

- Serum M protein (igG or igA) ≥ 30 g/L or uninary M protein ≥ 500 mg/24 hours and/or Absence of myeloma-defining events or amioidosis.



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Essential monoclonal gammopathy is defined by two key features: (1) the presence of a Essential monoclonal immunoglobulin in the serum or of monoclonal light chains in the urine and monoclonal evidence for an overt malignancy of a light chains in the urine and monoclonal light chains in the urine and the absence of evidence for an overt malignancy of B lymphocytes or plasma cells (2) the absence, myeloma or amyloidosis). (2) tile lymphoma, myeloma or amyloidosis).

Motor onal Gammopathy of Undetermined Significance (MGUS)

Marotest in serim < 30 g l

Bone marrow clonal plasma cells <10%

No evidence of other B cell proliferative disorders

Name on a related organ or tissue impairment (no end organ damage, including bone lesions) a

Assemptomatic Myeloma (Smoldering Myeloma)

Approton is serum >30 g L and/or

Bone marrow clonal plasma cells >10%

No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions a or symptoms

Symptomatic Multiple Myeloma

M protein in serum and/or urine

Bone marrow (clonal) plasma cellsb or plasmacytoma

Mean related organ or tissue impairment (end organ damage, including bone lesions).

Nonsecretory Myeloma

No M protein in serum and/or urine with immunofixation

is a marrow clonal plasmacytosis >10% or plasmacytoma

भू र अन्य related organ or tissue impairment (end organ damage, including bone lesions)a

V tart Plasmacytoma of Bone

No M protein in serum and/or urinec

Single area of bone destruction due to clonal plasma cells

Bone marrow not consistent with multiple myeloma

Sormal skeletal survey (and MRI of spine and pelvis if done)

Virtual organ or tissue impairment (no end organ damage other than solitary bone lesion)a

- a Myeloma-related organ or tissue impairment (end organ damage) (ROTI): Calcium levels increased: serum calcium >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L; renal insufficiency: creatinine >173 mmol/L; anemia: hemoglobin 2 g/dL below the lower limit of normal or hemoglobin <10 g/dL; bone lesions: lytic lesions or Osteoporosis with compression fractures (MRI or CT may clarify); other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months).
- b If flow cytometry is performed, most plasma cells (>90%) will show a "neoplastic" phenotype.
- c A small M component may sometimes be present.



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The most common clinical feature of multiple myeloma is anemia.

Myeloma bone disease is a major source of morbidity and may present as an area of persistent pain or as a vague migratory bone pain, often in the lower back and peivis. The type, location, and duration of the pain has no characteristic features. At times, pain and tenderness may be sudden in onset, especially when associated with a pathologic fracture, and is most commonly precipitated by movement. Persistent localized pain also may be associated with a pathologic fracture.

- 1. Myeloma cells adhere to stroma.
- 2. Stromal cells secrete OAFs.
- 3 OAFs induce stroma and osteoblasts to secrete RANKL.
- 4a RANKL is blocked by OPG, syndecan from MM cells traps and internalizes OPG.
- 4b. Excess RANKL is available to stimulate osteoclasts.
- 5. Increased cytokines stimulate myeloma cell growth.
- 6 These cytokines stimulate myeloma cell growth.
- These cytokines also cause release of PTHrP from MM cells, which activates stromal cells to secrete additional RANKL.

Chinical Finding	Underlying Cause and Pathogenetic Mechanism.
Hypercalcem a osteoporosis, pathologic fractures, lytic bone lesions, bone pain.	Tunior where the
Renal failure	Hypercalcemia, light chain deposition, amyloidosis, ura nephropathy, drug toxicity (nonsteroidal anti-inflammatory agen- bisphosphonates), contrast dye
Easy fatigue/anemia.	Bone marrow infiltration, production of inhibitory factor hemolysis, decreased red cell production, decreased erythroporet
Recurrent infections.	Hypogammaglobulinemia. low CD4 count, decreased neutroph
eurologic symptoms,	Hyperviscosity cryoglobulinemia, amyloid deposits, hypercalcemia therapy-related toxicity
ceding/clotting disorder	Renal failure, hypercalcemia
breviation: POEMS, polyneuropat	amyfold damage of endothelium, platelet dysfunction, antibody to clotting factors, oating of platelet, therapy-related hypercoagulable defects, thy, organomegaly, endocrinopathy, multiple myeloma, and skin



#### gnostic Criteria for Myeloma Requiring Therapy

Presence of an monoclonal immunoglobulin in serum and/or urine plus clonal plasma cells in the marrow and or a documented clonal plasmacytoma.

Plasone of more of the following:

(1) om elevation (\*11.5 mg dL) [>2.65 mmol/L]

Resultansafficiency (creatinine >2 mg/dL) [177 µmol/L or more]

Anemia (hemoglobin <10 g/dL or 2 g/dL <12.5 mmol/L‡ or 1.25mmol/L

B recesser lytic lesions or osteopenia)

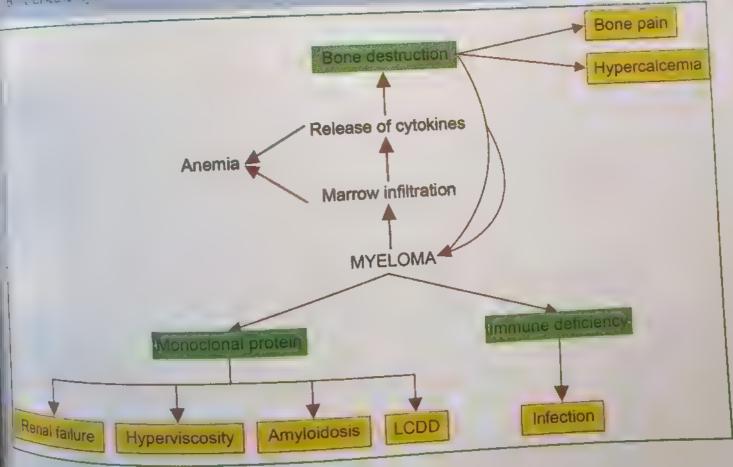


Fig. 18.6



Fig. 18.7 Punched out lesions in the skull



Fig. 18.8

Relatively normal-appearing plasma cells, plasmablasts with vesicular nuclear Relatively normal representation of plasmablasts with vesicular nuclear chromatin and a prominent single nucleolus, or bizarre, multinucleated cells may chromate.

other cytologic variants stem from the dysregulated synthesis and secretion of Ig, Other cytologic of intracellular accumulation of intact or partially degraded protein.

Anch often leads to intracellular accumulation of intact or partially degraded protein.

Such variants include flame cells with fiery red cytoplasm, Mott cells with multiple Such variants income droplets, and cells containing a variety of other inclusions, grape ke cytoplasmic droplets, and globules grape to fibrils, crystalline rods, and globules.

The globular inclusions are referred to as **Russell bodies** (if cytoplasmic) or **Dutcher** 

- Journal disease, plasma cell infiltrates may be present in the spleen, liver, dneys, lungs, lymph nodes, and other soft tissues.
- Commonly, the high level of M proteins causes red cells in peripheral blood smears to STICK to one another in linear arrays, a finding referred to as rouleaux formation.
- ROJ eaux formation is characteristic but not specific, in that it may be seen in other conditions in which Ig levels are elevated, such as lupus erythematosus and early HIV
- Rarely, tumor cells flood the peripheral blood, giving rise to plasma cell leukemia.
- . The trad tional age limit for autotransplantation is 65 years, although older patients should be considered for transplantation provided good organ function is present.
- Phys.o ogic rather than chronologic age is more suitable for determining transplantation
- The standard of care for elderly patients for many years has been melphalan and
- However, the introduction of the novel drugs thalidomide, lenalidomide, and bortezomib has changed the treatment paradigm for the elderly patient population.

# Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia:

- The median age at diagnosis is 60 years, and there is a 2:1 male predominance.
- · Delet ons in the long arm of chromosome 13 are the most common genetic abnormality n CLL, occurring in approximately half of all CLL cases.
- More than 25 percent of patients are asymptomatic at diagnosis. Such patients generally are detected because of the discovery of nontender lymphadenopathy or an unexplained absolute lymphocytosis. Otherwise, patients may have only mild symptoms of reduced exercise tolerance, fatigue, or mala se.
- Nearly 80 percent of all CLL patients have nontender lymphadenopathy at diagnosis, most commonly involving the cervical, supraclavicular, or axillary lymph nodes. The d agnosis of CLL requires a sustained monoclonal lymphocytosis greater than 5000/
- pL (5 x 109/L). Lymph nodes are diffusely effaced by an infiltrate of predominantly small lymphocytes 6 to 12 µm in diameter with round to slightly irregular nuclei, condensed chromatin, and scant
- Admixed are variable numbers of larger activated lymphocytes that often gather in loose aggregates referred to as **proliferation centers**, which contain mitotically active cells. When present, proliferation centers are pathognomonic for CLL/SLL.



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Some of these cells are usually disrupted in the process of making smears, producing so-called smudge cells.

SO-Calico Since					am.					1
Disease Entity	sIg	CD5	CD10	CDHe	CD19	CD20	CD22	CD23	CD25	CD103
Chronic lymphocytic leukemia	+/	44	~	-/+	+	+/-	-/+	++	-/+	-
Prolymphocytic leukemia	++	+/-		-/+	+	+/-	+	+/-	-	-
Hairy cell leukemia	+	- ,	<del>-</del>	++ 1	+ .	+	++	-/+	+	
Mantie cell lymphoma					+		÷			
Splenic marginal zone lymphoma	+	/+	e de la companya de l	4/-	+ . , 	,	+/	<b>-</b> [	-	-
Lymphoplasmacytoid lymphoma	/+	/+	The state of the s	American springs	+	+/-	+/-	/+	+/-	-
Folficular center lymphoma	+		+:		+ .	++ ,,,	+	<u>-/</u> +	-	-

R-VYCY-test Capting System				
Revised Staging Original C System Staging System		Clinical Features at Diagnosis	Median Survival.   Years*	
Low risk	0	Blood and marrow lymphocytosis	12	
	1	Lymphocytosis and enlarged lymph nodes	11	
Intermediate risk	II	Lymphocytosis and enlarged spleen and or liver.	8	
High risk	1(1	Lymphocytosis and anemia (hemoglobin below 11 g/dL).	5	
	IV	Lymphocytosis and thrombocytopenia (platelets below 100,000/L).		



Stage

# Chincal Features at Diagnosis

Median Survival, Years

- Blood and marrow tem phoeytosis and less than 3 areas? of pup, ble capi die fissie en argement
- Bood and marrow lymphocytosis and 3 or more areas of palpable lymphoidissue on traement
- Sans is B with anomia the moglobin below 11 g dL in men or 10 g il in women) or thrombocytopenia (platelets less than 100,000 pl.

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The absent openia

news reated symptoms

Market v enlarged or painful spleen

so intomatic symphadenopathy

Base yapprocyte count doubling time <6 months

ne mp neytic transformation

- Patients whose presentation is typical B cell CLL with no manifestations of the disease other than bone marrow involvement and lymphocytosis (i.e., Rai stage 0 and Binet stage A) can be followed without specific therapy for their malignancy. These patients have a median survival >10 years, and some will never require therapy for this disorder.
- Patients who present with bone marrow failure (i.e., Rai stage III or IV or Binet stage
- The most common treatments for patients with typical B cell CLL/small lymphocytic lymphoma have been chlorambucil or fludarabine, alone or in combination. Chiorambucii can be administered orally with few immediate side effects, while fludarabine is administered IV and is associated with significant immune suppression. However, fludarabine is by far the more active agent and is the only drug associated with a significant incidence of complete remission.
- Mycosis fungoides and Sézary syndrome are different manifestations of a tumor of
- Two different clinical types of malignant T-cell disorders were originally recognized:
   Two different clinical types of malignant T-cell disorders were aggressive nodular. mycosis fungoides, a chronic proliferative process; and a more aggressive nodular
- Clinically, the cutaneous lesions of mycosis fungoides typically progress through three somewhat distinct stages, an inflammatory premycotic phase, a plaque phase, and a tumor phase.



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Histologically, the epidermis and upper dermis are infiltrated by neoplastic T cells, Histologically, the epidermis and upper definition of the nuclear which often have a cerebriform appearance due to marked infolding of the nuclear



Fig 16.9 Cutaneous T cell lymphoma. A. Several ill-defined, erythematous, often scaling, and occasionally ulcerated plaques B, Microscopically, there is an infiltrate of atypical lymphocytes that show a tendency to accumulate beneath the epidermal layer and to invade the epidermis.

- Late disease progression is characterized by extracutaneous spread, most commonly to lymph nodes and bone marrow.
- Sézary syndrome is a variant in which skin involvement is manifested as a generalized exfoliative erythroderma. In contrast to mycosis fungoides, the skin lesions rarely proceed to tumefaction, and there is an associated leukemia of "Sézary" cells with characteristic cerebriform nuclei.
- The histologic hallmark of CTCL of the mycosis fungoides type is the presence of the Sézary-Lutzner cells. These are T-helper cells (CD4+) that characteristically form band-like aggregates within the superficial dermis and invade the epidermis as single cells and small clusters (Pautrier microabscesses).
- These cells have markedly infolded nuclear membranes, imparting a hyperconvoluted
- Although patches and plaques show pronounced epidermal infiltration by Sézary-Lutzner cells (epidermotropism), in more advanced nodular lesions the malignant T cells often lose this epidermotropic tendency, grow deeply into the dermis, and eventually spread systemically.
- The tumor cells characteristically express the adhesion molecule CLA and the chemo-CD4+ T college to the and CCR10, all of which contribute to the homing of normal
- Although cutaneous disease dominates the clinical picture, sensitive molecular analyses have shown that the dominates the clinical picture, sensitive molecular lymph nodes even control the tumor cells circulate through the blood, marrow, and lymph nodes even early in the course. Nevertheless, these are indolent tumors, with a median survival of 8 to 9 years. Transformation to aggressive T-cell lymphoma occurs occasionally as a terminal event.
- Topical therapy with steroids or UV light is often used for early lesions of CTCL, whereas more aggressive such as the steroids of UV light is often used for early lesions of CTCL, and disease. whereas more aggressive systemic chemotherapy is indicated for advanced disease.

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Non Hodgkins Lymphomas (Nhl) Revision Points: Not common form of NHL - diffuse large B cell lymphoma MOST common extra nodal site of NHL - stomach > CNS

MOST ymphoid neoplasms are of B cell origin (85-90%). Most your site of endemic Burkitt's lymphoma - jaw or mandible Most common site of sporadic burkitt lymphoma is ileocaecum or peritoneum.

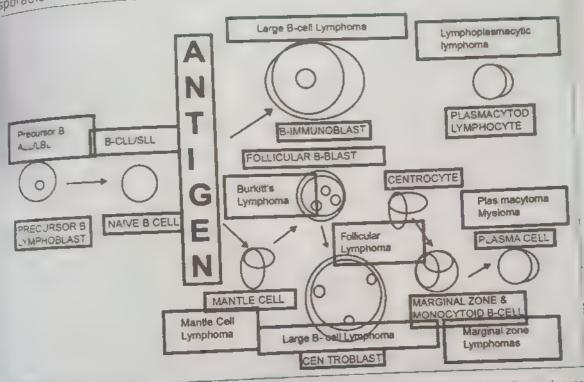


Fig. 18.10. Schema of B-ceil differentiation, showing postulated normal counterpart of B-cell neoplasms

#### Lymphomas in HIV AIDS:

Predominantly aggressive B cell lymphomas.

Most common include.

- burkitts lymphoma.
- · DLBCL.
- primary effusion lymphoma (especially associated with HHV 8).
- plasmablastic lymphoma.
- Hodgkin's lymphoma (unexpected increase after HAART).

Role of EBV (40%) and HHV 8 Disruption of cytokine network leading to high levels of I\_ 6 and IL 10- a feature of HIV related lymphomas associated with EBV and HHV 8.

Plastia cel

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# THE THE PERSON NAMED IN

#### **Active Recall**

Cunical features Pathology / Markers Treatment & prognosis

1.1

Barkitt lymphoma

CLL SLL

Follicular Lymphoma

Mantle cell lymphoma

Marginal zone lymphoma

Mycosis fungoides

Plasma cell neoplasm

Hairy cell leukaemia

Diffuse large B cell lymphoma



# HODGKIN'S LYMPHOMA

# CONCEPTS

- Censept 19:1: Hadgian's Lymphama



#### Concept 19.1: Hodgkin's Lymphoma

Concept 19.1: Houghing Cylinical features, markers, associations, prognosis

#### Time Needed

I family	60 mm
2 <sup>nd</sup> reading	30 min

- From a historical point of view, HL was the first cancer in which the curative potential
- Second, because affected patients are often young, there is a great potential for
- Third, because patients with HL are often cured, HL serves as a clinical laboratory for
- HL usually presents as solitary or generalized lymphadenopathy and most commonly occurs in young adults, although any age group may be affected.
- The disease appears to spread in a contiguous fashion, and most patients present with disease limited to the lymph nodes or to the lymph nodes and spleen.
- Even when the disease is advanced, cure is possible.
- Overall, cure can be achieved in approximately 80% of patients with HL.
- Treatment of limited disease often incorporates radiation therapy and combination chemotherapy, whereas treatment of advanced disease is generally limited to combination chemotherapy alone.

#### Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification):

6	Distribution of Disease
1	Involvement of a single lymph node region (1) or a single extra-lymphatic organ or site (IF
11	Involvement of two or more lymph node regions on the same side of the diaphragm alone llict localized involvement of an extra-lymphatic organ or site (IIE).
111	Involvement of lymph node regions on both sides of the diaphragm without (III) or with (III) localized involvement of an extra-lymphatic organ or site.
IV	Diffuse involvement of one or more extra-lymphatic organs or sites with or without lymphatic involvement.

Pathologically, HL is distinguished from other lymphomas by the presence of large binucleated or multinucleated cells (i.e., Reed-Sternberg cells) generally surrounded by a benign reactive host response consisting of lymphocytes, histiocytes, granulocytes, eosinophils, and plasma cells.

Reed-Sternberg cells are large cells with abundant cytoplasm and generally contain two or more nuclei and two or more inclusion like nucleoli.





Fig. 19.1

Reed-Sternberg cells are not absolutely specific for HL and have been noted in cases of infectious mononucleosis and other malignancies including lymphoma, carcinomas, and sarcomas

## The WHO classification recognizes five subtypes of HL:

- \odular sclerosis
- Mixed cellularity
- ; Lymphocyte-rich
- Lymphocyte depletion
- Lymphocyte predominance

In the first four subtypes—nodular sclerosis, mixed cellularity, lymphocyte-rich, and ymphocyte depletion—the Reed-Sternberg cells have a similar immunophenotype. These subtypes are often lumped together as **classical** forms of HL. In the remaining subtype, lymphocyte predominance, the Reed-Sternberg cells have a distinctive B-cell mmunophenotype that differs from that of the "classical" types.

# Classification of Hodgeth Lymphoma Immunopheno type Vod Jar lymphocyte-predominant Classical CD20+ CD30+ CD15+ lg CD20-\* CD30+ CD15+ lg Nodular scierosis Mixed cellularity Lymphocyte-rich Lymphocyte-depleted

- -ymphocyte-predominant HL is associated with the least tendency to have advanced disease and with the most favorable prognosis, whereas lymphocyte-depleted HL is associated with the greatest tendency to have advanced disease and the worst prognosis.
- Nodular sclerosing HL and mixed cellularity HL are intermediate in this regard, with nodular sclerosing HL being more favorable than mixed cellularity HL.



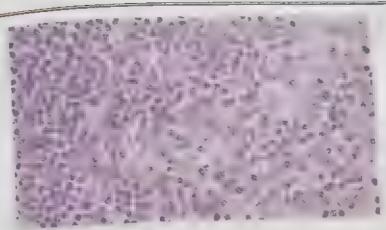
PATHOLOGY

Subtypes of	Hodgkin Lymphoma:  Morphology and Immunopheno type	Typical Clinical Features
Nodular sclerosis	Trequent laction cens and occasional magnosic RS cells, background infiltrate composed of T lymphocytes, eosinophils, macrophages, and plasma cells; fibrous bands dividing cellular areas into nodules. RS cells CD15+, CD30+; usually EBV-	Most common subtype, usually stage I or II disease, frequent mediastinal involvement, equal occurrence in males and females (F = M), most patients young adults.
Mixed cellularity	Frequent mononuclear and diagnostic RS cells; background infiltrate rich in T lymphocytes, eosinophils, macrophages, plasma cells; RS cells CD15+, CD30+; 70% EBV+	More than 50' o present as stage III or IV disease; M greater than F, biphasic incidence, peaking in young adults and again in adults older than 55.
Lymphocyte rich	Frequent mononuclear and diagnostic RS cells; background infiltrate rich in T lymphocytes; RS cells CD15+, CD30+; 40% EBV+	Uncommon; M greater than F; tends to be seen in older adults.
Lymphocyte dep'etion	Reticular variant: Frequent diagnostic RS cells and variants and a paucity of background reactive cells; RS cells CD15+, CD30+; most EBV+	Uncommon: more common in older males, HIV-infected individuals, and in developing countries, often presents with advanced disease.
ymphocyte predominance	Frequent L&H (popcorn cell) variants in a background of follicular dendritic cells and reactive B cells: RS cells CD20+, CD15-, C30-; EBV-	Uncommon: young males with cervical or axillary lymphadenopathy; mediastinal

L&H. lymphohistiocytic: RS cell. Reed-Sternberg celi:



Fig. 19.2: Nodular sclerosing hodgkin lymphoma. High magnification shows Reed-Sternberg cells and lacunar variants in B5 fixed material.



Mixed cellularity-type Hodgkin lymphoma. High magnification shows a classic Reed-Stemberg ceil in a mixed background of small lymphocytes, plasma cells, and eosinophils.



Fig. 19.4 Lymphocyte-depleted type hodgkin lymphoma, diffuse fibrosis subtype. Reed-Sternberg cellularity and composed of amorphous eosinophilic cells are esally foun, and the background is depleted of cellularity and composed of amorphous eosinophilic connective tissue.

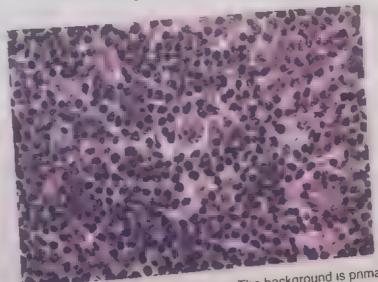


Fig 19.5 Lymphocyte-rich "classic" Hodgkin lymphoma. The background is primarily lymphocytes, and the Reed Sternberg cells are usually CD1S+ and CD30+ and negative for the B-cell marker CD20.





Fig. 19.6 Lymphocyte-predominant Hodgkin lymphoma. High magnification shows variant lymphocytic and histocytic cells (L and H cells), which have "popcorn" nuclei. A background of small lymphocytes and his tiocytes is present.

History and physical examination.

Special attention to history of B symptoms (i.e., fever, night sweats, weight loss of >10% in past 6 mo)

Examination of all peripheral lymph node regions, liver, and spleen.

Radiologic studies.

Chest radiograph.

CT scan of thorax.

CT scan of abdomen and pelvis.

PET scan.

Laboratory studies.

Hematocrit, white blood cell count, differential, platelet count.

Erythrocyte sedimentation rate (optional).

Blood urea nitrogen, creatinine.

Bilirubin, alkaline phosphatase, lactic dehydrogenase, "hepatocellular" enzymes.

Bone marrow aspiration and biopsy (optional)

CT, computed tomography, PET, positron emission tomography.

Patients with localized Hodgkin's disease are cured >90% of the time. In patients with good prognostic factors, extended-field radiotherapy has a high cure rate.

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# ACUTE MYELOGENOUS LEUKEMIA

# CONCEPTS

= Concept 20.1: Acute Myelogenous Leukemia

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## Final Revision Points for Hodgkin's Lymphoma; Most common Hodgkin's lymphoma - nodular sclerosis.

Most common HL in India mixed cellularity

Most common HL in western countries - nodular sclerosis.

Least common HL lymphocyte depleted.

Maximum RS cells - mixed cellularity.

Minimum RS cells - lymphocyte rich. Best or most specific marker for classical RS cells - CD 30.

Most sensitive marker- CD 15.

Most sensitive intalker

Best prognosis - lymphocyte predominant followed by nodular sclerosis. Worst prognosis Best prognosis - lymphocyte prognosis - lymphocyte depleted. EBV frequency is maximum in - mixed cellularity.

EBV frequency minimum in - nodular sclerosis.

## General Points about Hodgkin's Lymphoma:

- 1. Mostly cervical lymph nodes are involved.
- 2. Seen in young adults.
- 3. Large monocuclear/multinucleated tumor cells (RS cells) in abundant heterogenous mixture of non-neoplastic inflammatory and accessory cells.
- 4. Often ringed by T cells in a rosette like manner.
- 5. Constitutes ~30% of all lymphomas.
- 6. Classified into Nodular Lymphocytic Predominant HL and Classical HL.

#### Classical HL:

- 95% of HL.
- bimodal presentation: 15-35 years and in late life.
- · patients with Infectious Mononucleosis have a higher incidence.
- · 75% cases present with cervical lymph nodes followed by mediastinal, axillary and paraortic.
- 60% patients have localized disease.
- 40% patients have B symptoms.
- CD 30+ in all cases.
- CD 15+ in 75-85% cases.
- CD 45 in all cases.
- maximum EBV in mixed cellularity (75%).
- minimum EBV in nodular sclerosis (10-40%),.

# Nodular Lymphocyte Predominant Hodgkin Lymphoma:

- large neoplastic cells called Popcorn or LP or LH cells.
- 5% of HL.
- mostly in Males.
- most frequently in 30-50 years age group.
- latent EBV infection is consistently absent from LP cells.
- CD 20/79a/75/45 positive, BCL 6 positive.

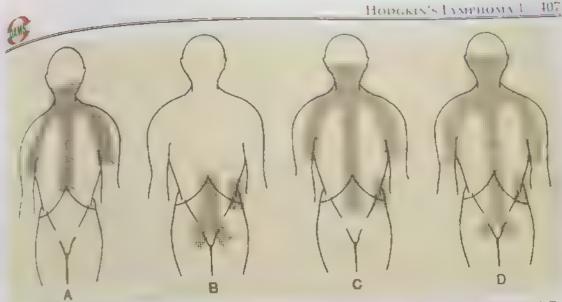


Fig. 19.7 Treatment fields used as extended field irradiation of Hodgkin disease. A. Mantel field B. nverted Y field C. Mantle and para-aortic field (extended mantle field) D. Total nodal field. The spleen is irrad ated in conjunction with the fields in B, C, and D, unless it has been surgically removed

Increasingly, patients with all stages of Hodgkin's disease are treated initially with chemotherapy. Patients with localized or good-prognosis disease receive a brief course of chemotherapy followed by radiotherapy to sites of node involvement. Patients with more extensive d sease or those with B symptoms receive a complete course of chemotherapy. The most popular chemotherapy regimens used in Hodgkin's disease include doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), or combinations of the drugs in these two regimens. Today, most patients in States receive ABVD, but a weekly chemotherapy regimen admin stered for 12 weeks the United called **Stanford V** is becoming increasingly popular, but includes radiation therapy, which has been associated with life threatening late toxicities such as premature coronary artery disease and second solid tumors.

GELLE	mature coronary artery disease and second some
Stage	Therapeutic Options.
IA and IIA	Combination chemotherapy.  Abbreviated combination therapy (e.g. four cycles ABVD) plus involved field radiation therapy
	Abbreviated combination therapy (e.g. tour cycles
	Extended field radiation therapy
	Involved field radiation therapy.
IB and IIB	Combination chemotherapy plus involved field radiation.
	a landaria
	Extended field radiation therapy plus combination chemotherapy.
	= to the thorac
IX and IIX	Combination chemotherapy with involved field radiation therapy.
	Combination chemotherapy
IIIA, IIIB, IVA, and	Combination chemotherapy
L/B	to the third masses
	thorage with radiation boost to large tumor masses

Combination chemotherapy with radiation boost to large tumor masses



## Concept 20.1: Acute Myelogenous Leukemia

Learning Objectives: CD marker, Morphology genetics & prognosis of leukaemia.

#### Time Needed

1 reading	60 min
2 reading	30 mm

Phenotypel	
Myeloblastic	CD116, CD13, CD15, CD33, CD117, HLA-DR
Myclomonocytic	CD716, CD13, CD14, CD15, CD32, CD33, HLA-DR
inthrod	Glycophorin, spectrin, ABH antigens, carbonic anhydrase I, HLA-DR
Promyelocytic	CD13, CD33
Monocytic	CD11b, 11c, CD13, CD14, CD33, CD65, HLA-DR
Megakaryoblastic	CD34, CD41, CD42, CD61, anti-von Willebrand factor
Basophilie	CD11b, CD13, CD33, CD123, CD203e
Mast ceil	CD13, CD33, CD117

## WHO 2017 update of AML classification.

AML with recurrent genetic abnormalities

AML with t (8;21) (q22;q22.1); RUNX1-RUNX1TI

AML with inv (16) (p"13 1 q22) Ort (16,-16) (p13.1:q22); CBFB-MYH11

APL with PML-RARA

AML with t (9:11)(p2l.3m23J3):MLLT3-KMT2A

AML with (6.9) (p23.q34.1); DEK-NLP214

AML with inv (3) (q21\_3q26\_2) or t (3:3) (q21\_3: q26\_2); GATA2. MECOM

AML (megakaryoblastic) with t (1.22)(pi3.3gq 13L3); RBM15-MKL1

Provisional entity, AML with BCR-ABL1

AML with mutated NPMI

AML with biallelic mutations of CEE3PA

Provisional entity. AML with mutated RUNXI

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML NOS

AML with minimal differentiation

AML without maturation



AML with maturation

Acute myelomonocytic leukemia Auste menoblastic / monocytic leukemia

Pure erythro dieukemia

Avec megakaryoblastic leukenna

Your hasophilic leukemia

Acre paging elosis with myelofibrosis

Wellad sale ama Myeloid practeral ons related to Down syndrome

Transient abnormal myelopoiesis (TAM)

weloid leukemia associated with Down syndrome

5gns and symptoms that signal the onset of AML include pallor, fatigue, weakness, 5 and dyspnea on exertion. The signs and symptoms reflect the development paptations, however, weakness, loss of sense of well-being, and fatigue on exertion can be disproportionate to the severity of anemia.

Easy bruising, petechiae, epistaxis, gingival bleeding, conjunctival hemorrhages, and pro onged bleeding from skin injuries reflect thrombocytopenia and are frequent early

Skin nvolvement may be of three types: nonspecific lesions, leukemia cutis, or granulocytic (myeloid) sarcoma of skin and subcutis.

AML with t (8;21), t (15;17), t (16;16) or inv (16) - are diagnosed as AML irrespective of blast count (AIIMS question).

# Major Subtypes of Aml in the Who Classification:

ajor Subtypes of A	III III tito I	EAB Subrype.	Na photographic Contraction
l. Aml with Genetic Aberr	ations		Full range of myelocytic maturation; Auer
AML with t (8;21) (q22;q22); CBFa/ETO	Favorable	M2	granules.
AML with inv(16) tp13;q22); CBFβ. MYH11 fusion gene.	Favorable	M4eo	abnormal basophilic granules.
AML with t (15:17) (q22 11-12), RARa PMI Iusion gene	Intermediate	M3. M3v	Numerous Auer rods, offer within individual programulocytes; primary granules usually very prominent (M3 subtype), but inconspictious in microgranula variant (M3v), high incidence of DIC.  Usually some degree of monocyti
AMic with t (11q23.v.); diverse MLL fusion genes	Poor	M4, M5	differentiation
A All, with normal cytogenetics and mutated NPM.	Favorable	Variable	Detected by staining for NPM.

II. Aml with Mds-Lik	e Features.		
With prior MDS	Poor	Variable	Diagnosis based on clinical history.
AML with multilineage dysplasia	Poor	Variable	Maturing cells with dysplastic features typical of MDS.
AML with MDS-like cytogenetic aberrations.	Poor	Variable	Associated with 5q-, 7q-, 20q-aberrations,
HI, AMI, THERAPY- RELATED.	Very por	Variab e	therapy, 2 to 8-year latency period, MDS like cytogenetic aberrations (e.g., 5q., 7q) if following topoisomerase II inhibitor (e.g. translocations involving MLL (11q23).
IV. Aml, Not Otherwise	Specified.	ماندمان کیارد در در در	and the second s
AML, minimally differentiated.	Intermediate	Mu	Negative for myeloperoxidase; myelon antigens detected on blasts by flow cytometry.
AML without maturation	. Intermediate	M1	>3% of blasts positive myeloperoxidase.
AML with myelocytic maturation	Intermediate	M2	Full range of myelocytic maturation
AML with myelomonocytic maturation.	Intermediate	M4	Myelocytic and monocytic different at a
AML with monocytic maturation.	Intermediate	M5a, M5b	In M5a subtype, nonspecific esteras positive monoblasts and pro-monocyt predominate in marrow and blood; in M5 subtype, mature monocytes predominate in the blood.
ML with erythroid aturation.	Intermediate	M6a, M6b	Erythroid mye,oid subtype Modefined by >50°, dysplastic mater erythroid precursors and >2° myeloblasts, pure erythroid subty (M6b) defined by >80° erythroid precursors without myeloblasts.
AL with gakaryocytic uration.	Intermediate	M7	Blasts of megakaryocytic linear predominate; detected with antibodi against megakaryocyte-specific market (GPIIb/IIIa or vWF); often associate with marrow fibrosis; most common AN

in Down syndrome. The diagnosis of AML is based on the presence of at least 20% myeloid blasts in the bone marrow.

- Several types of myeloid blasts are recognized, and individual tumors may have more several type of blast or blasts with hybrid features Several type of blast or blasts with hybrid features
- Myeloblasts have delicate nuclear chromatin, two to four nucleoli, and more Myeluminous cytoplasm than lymphoblasts
- voluntilities of the contains fine, peroxidase-positive azurophilic granules. Aver rne cytop ost.

  The cytop ost. rods distinction and solded on lobulated (15;17) (acute promyelocytic leukemia).
- Monoblasts have folded or lobulated nuclei, lack Auer rods, and are nonspecific Montos.

  Montos.

  Posterase-positive. In some AMLs, biasts show megakaryocytic differentiation, which is often accompan ed by marrow fibrosis caused by the release of fibrogenic cytokines.
- Rarely, the blasts of AML show erythroid differentiation.
- The number of leukemic ceils in the blood is highly variable. Blasts may be more than 100,000 per mm<sup>1</sup>, but are under 10,000 per mm in about 50% of patients.
- , Occasionally, blasts are entirely absent from the blood (aleukemic leukemia) For this reason, a bone marrow examination is essential to exclude acute leukemia in pancytopenic patients.

## Early blast clearance during remission induction therapy

Lenkemic cells contain t (8;21), t (15;17), inv (16) t (16;16), trisomy 21.

CEBPA mutations in cytogenetically normal AML.

Absence of exaggerated dysmyelopoiesis.

Residua, normal metaphases admixed with clonal cytogenetic abnormalities.

High telomerase activity levels.

Low levels of IdT expression by flow cytometry (<500)

High BAX expression and high BAX/BCL-2 ratios.

High expression of integrin CD11b.

Absence of VLA-4 expression on AML blast cells.

h gh levels of soluble VC AM-1 binding to AML blast cells

High levels of caspase-3.

Mutant CEBPA expression.

NPM, gene expression in adults or children (usually present in cytogenetically normal cases)

Higher neutrophil and higher platelet counts at time of complete remission

So hasts on day 14 marrow predicts for complete remission but not for overall survival

#### Paris, or

the states of the exclusive of the neonatal period, have the httphase the figure in patients older than age 60 years have only half the strate of the free dission, patients older than age 60 years have only half the chance of and less takelihood of a long relapse-free remission. There is Tyoung added the treatment through adulthood, with the largest decrease after the sixth decade of his Tyoung added. Crief to the sixth decade of life to the set of the sixth decade of life to the set of the set o

I mayorable karyotypes. The cytogenetic pattern of leukemic blast cells influences (at one but provide Largeopes. The eyrogeness of 5-, 7-, 5q-, 7q-, or of exagrerated hyperdiploids.

The presence of 5-, 7-, 5q-, 7q-, or of exagrerated hyperdiploids.

47 set the execute of resourced and multiple chronics small abnormal ties in eakemic cel sate power grostic signs

resistance pnenotype: Leukemic cells expressing P-glycoprotein, a unidirectional drug efflux resistance phenotype. Leakerson of this gene product can result in decreased accumulation of the model by the MDR1. Expression of this gene product can result in decreased accumulation of the control of the model the same amsacrine, mitoxantrone, and etoposide. Expression of P-glycoprotein does not influence the same amsacrine, mitoxantrone, and etoposide. Expression of P-glycoprotein does not influence the same amsacrine, mitoxantrone, and etoposide. describes amsacrine, hittoxandrone, 123 efflux also is increased, relapse is more common. Frequently also is increased treatment, but if thodamine-123 efflux also is increased, relapse is more common. Frequently ato not it treatment, but it induating the control of the control AML cells after relapted to the mechanisms are important also MDR1 expression is tow in favorable prognosis subtypes of AML.

Presence of mutated KIT with 1 (8:21): Associated with higher relapse risk and poorer overall survival

Prior clonal hemopathy. Chemotherapy or radiotherapy remission rates are one-third to one-half that of de-Phot clonal hemopathy Chemotherapy of that of de novo AML in the same age group. Remission duration is shorter with remissions >3 years very uncommon AML developing from the clonal hemopathy may relapse as a smoldering leukemia. It then reverts to AML but can be treated with remissions lasting several years

Higher white cell count Count >30,000, µL (30 x 109.1) or a blast cell count >15,000/µL (>15 x 109 L) Very low platelet count (<30,000 µL [<30 x 109,1])

H gh serum lactic dehydrogenase.

High stem cell mobilizing capacity during complete remission predicts for relapse risk.

Another medical disorder, extreme obesity, diabetes mellitus, chronic renal disease

Low serum albumin or prealbumin.

Need for intubation or ventilator support during induction therapy.

Actonomous clonal growth of leukemic blast cells

High BCL-2 expression.

High MCL-1 expression. Elevated at the time of leukemic relapse. Suggests prognostic importance or that chemotherapeutic regimen selects for leukemia cells with elevated levels of apoptosis inhibitors Low expression of retinoblastoma gene.

High levels of WAF-Cipl protein. This is a regulator at the G1 checkpoint of cell cycle.

High (D34 expression High CD34 antigen expression often in AML subtypes M0, M1, and M4 Remission to the state of the state expression of CD34 and Line AML not expressing CD34. Correlation is stronger between high-intensity expression of CD34 and lower remission rate. CD34 expression in APL. GAIA-1 expression

Neural cell adhesion molecule (CD56) expression.

Elevaled soluble L-selectin. Seen especially in extramedullary disease

Their expression of interleukin-18 gene

Types on at the thrombopoiet is receptor (c-MPL) mRN (

burnesed angiogenesis/vascular endothelial growth factor levels.

High \(\beta^2\)-microglobulin levels in adults younger than 60 years old Not (meningioma 1) gene overexpression in AML patients with normal cytogenetics.

Young adults with the genotype WT1 (mutation)/FLT3-ITD(positive) have a lower complete remission Young and inferior re appertice and overall survival compared to those with the genotype WT1(mutation)/ FLT3-ITD(negative)

WII gene mutations in patients with AML and a normal karyotype.

Patients with AMI with a large number of AMI stem cells

Elevated expression of IL-3Ra.

MLL tandem duplications and 11p23/MLL abnormalities.

CD56 expression in APL. High incidence of CNS involvement, especially with CD7 expression. Also contributes to poorer outcomes in t (8;21) cases.

P15 methylation.

Microsatellite instability (may not be independent of age and t-AML).

40 33 expression (shorter remissions and disease free survival)

Constitutive activity of signal transducer and activator of transcription 3 protein (shorter disease-free

BAALC gene expression.

It an S-phase activity in cells surviving after 7 days of induction.

Hen EVII expression.

Overexpression of CXCR4.

thereased marrow angiogenesis as measured by magnetic resonance imaging.

The presence of the CTLA4 CT60 A G genotype adult patients with AML.

Chromosome findings at diagnosis are currently the most important independent prognostic factor. Patients with t (15;17) have a very good prognosis (approximately 85% cured), and those with t (8;21) and inv (16) a good prognosis (approximately 55% cured), while those with no cytogenetic abnormality have a moderately favorable Outcome (approximately 40% cured). Patients with a complex karyotype, t (6;9), inv (3), or -7 have a very poor prognosis.

#### Treatment:

1211

- The most commonly used CR induction regimens (for patients other than those with APL) consist of combination chemotherapy with cytarabine and an anthracycline.
- Cytarabine is a cell cycle S-phase-specific antimetabolite that becomes phosphorylated ntracellularly to an active triphosphate form that interferes with DNA synthesis.

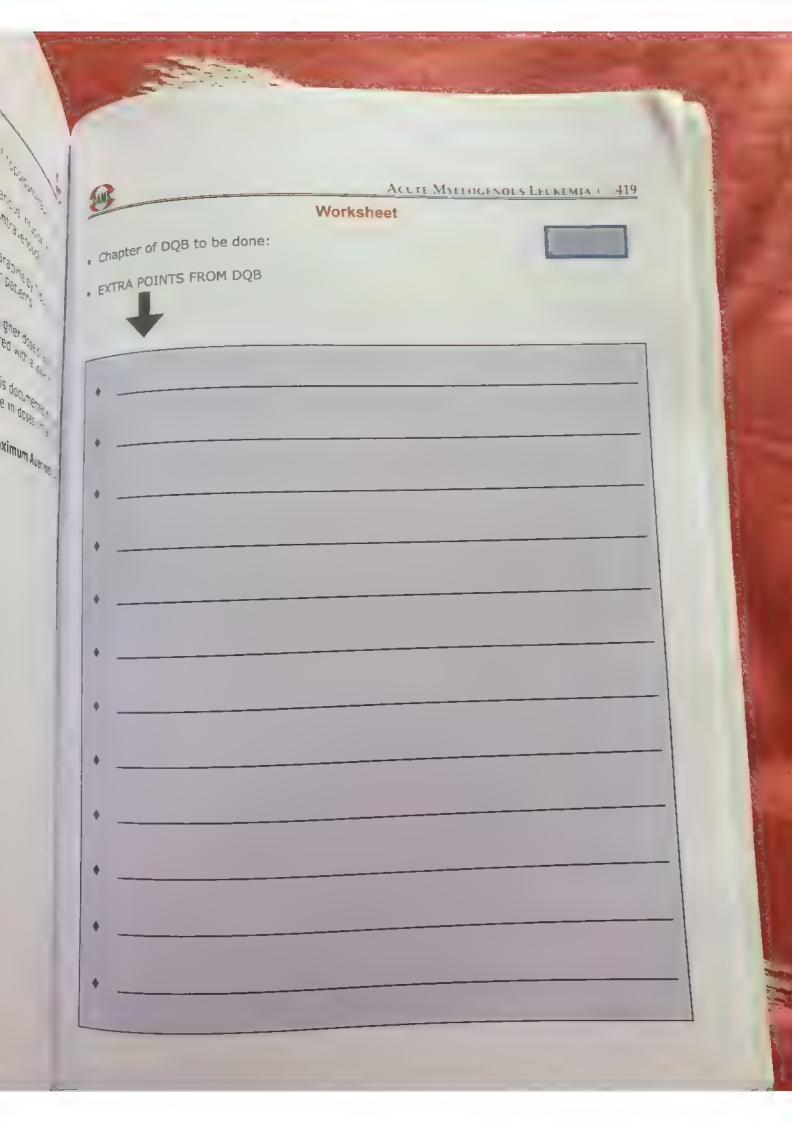
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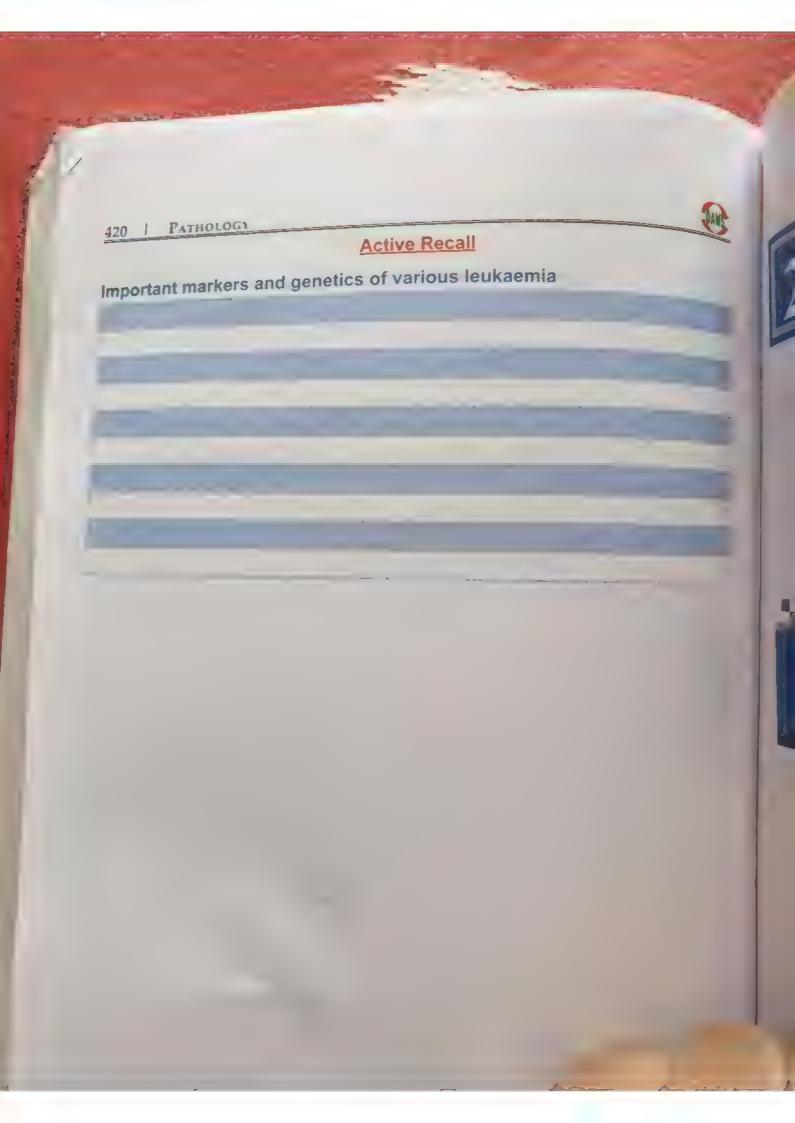


Cr

- Anthracyclines are DNA intercalators.
- Their primary mode of action is thought to be inhibition of topoisomerase II, leading to DNA breaks.
- Cytarabine is usually administered as a continuous intravenous infusion for 7 days.
- Anthracycline therapy generally consists of daunorubicin intravenously on days 1, 2, and 3 (the 7 and 3 regimen).
- Treatment with idarubicin for 3 days in conjunction with cytarabine by 7-day continuous infusion is at least as effective as daunorubicin in younger patients.
- The addition of etoposide may improve the CR duration.
- When combined with cytarabine in a 7 and 3 regimen, a higher dose of anthracycline (i.e., daunorubicin 90 mg/m²) improves outcome compared with a lower dose (i.e., daunorubicin 45 mg/m²).
- After induction chemotherapy, if persistence of leukemia is documented, the patient is usually re-treated with cytarabine and an anthracycline in doses similar to those given initially, but for 5 and 2 days, respectively

AML with best prognosis, highest incidence of DIC, maximum Auer rods: APML (M3) (\*).



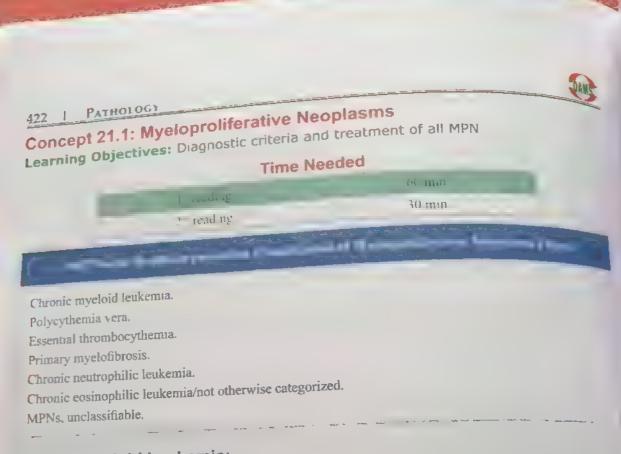




# MYELOPROLIFERATIVE NEOPLASMS

# CONCEPTS

Concept 21 1 Myeloproliferative Neoplasms



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#### Chronic Myeloid Leukemia:

- Chronic myeloid leukemia (CML) is the classic chronic myeloproliferative disorder.
- It is a clonal stem cell disorder characterized by the acquisition of an oncogenic BCR/ ABL fusion protein [usually the result of a reciprocal translocation (9;22) q34;q11)] and by proliferation of granulocytic elements at all stages of differentiation.
- The t(9;22) is also referred to as the Philadelphia chromosome (Ph), in honor of the city in which it was identified by Nowell and Hungerford in 1960.

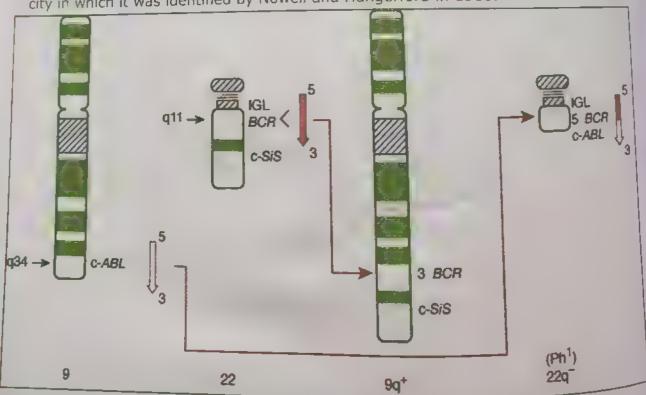


Fig. 21.1

5chematic of normal chromosome 9 showing the ABL gene between band q34 schematic of chromosome 22, which has the BCR and SIS genes between band q34 and qter. The t(9;22) is shown on the right. The total and other states and other states are states and other states. and qter of the t(9;22) is shown on the right. The ABL from chromosome gil and quelle and the chromosome 22 M-bcr sequences, and the terminal of chromosome 22 is transposed to the leaves and the terminal 9 15 transposed to the long arm of chromosome 9.

portion of chromosome. bcr. breakpoint clust portion of the Ph chromosome. bcr, breakpoint cluster region; c-SiS, cellular the 22q- is the viral simian sarcoma virus-transfer region; c-SiS, cellular the 229 is of the viral simian sarcoma virus-transforming gene; IGL, gene for a clabulin light chains. mmunoglobulin light chains.



Fig. 21.2

Fluorescence in situ hybridization for BCR/ABL using a dual-color, dual-fusion probe set - Positive for BCR/ABL fusion. Typical abnormal pattern with one red, one green, and two fused (yellow) signals.

CML is often referred to as the disease of "firsts". It was the first disease.

a. in which the term leukemia was utilized,

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1960

- b to be associated with a consistently recurring chromosomal abnormality,
- to be recognized as the result of material reciprocally translocated from one
- d to be the direct result of a specific gene fusion (as a result of the translocation), and
- e. to have a therapy particularly targeted against the fusion protein.
- The most frequent complaints include easy fatigability, loss of sense of well-being, decreased tolerance to exertion, anorexia, abdominal discomfort, early satiety (related to spienic enlargement), weight loss, and excessive sweating.
- A physical examination may detect pallor and splenomegaly. The latter was present n approximately 90 percent of patients at diagnosis
- Elevated white blood (cell) counts (WBCs), with increases in both immature and
- Usually <5% circulating blasts and <10% blasts and promyelocytes are noted, with mature granulocytes, are present at diagnosis. the majority of cells being myelocytes, metamyelocytes, and band forms.
- Cycling of the counts may be observed in patients followed without treatment.



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• Platelet counts are almost aiways elevated at diagnosis, and a mild degree of platelet counts are almost always elevated. Leukocyte alkaline phosphatase is low in CML cells.

• Phagocytic functions are usually normal at diagnosis and remain normal during the

chronic phase.

Chronic phase.

Histamine production secondary to basophilia is increased in later stages, causing

pruntus, diarrhea, and flushing.



Fig. 21.3

Disease acceleration is defined by the development of increasing degrees of anemia unaccounted for by bleeding or therapy; cytogenetic clonal evolution; or blood or marrow blasts between 10 and 20%, blood or marrow basophils >20%, or platelet count <100,000/µL. Blast crisis is defined as acute leukemia, with blood or marrow biasts >20%. Hyposegmented neutrophils may appear (Pelger-Huet anomaly). Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated, based on morphologic, cytochemical, and immunologic features.

## Diagnosis of Accelerated and Blast Phase in CMLa

Accelerated phase

Blasts 10-19% in the peripheral blood and/or bone marrow

Basophils ≥20% in the peripheral blood

Persistent thrombocytopenia

Increasing spleen size and white blood cell count despite therapy

Cytogenetic evidence of clonal evolution

Blast phase

Blasts -20%,

Larranged diary plast proinferation

Large aggregates or clusters of plasts in the bone marrow.

#### Treatment:

• Imatinib mesylate (imatinib) is now used as initial therapy in almost all patients with

In cases where the white cell count 's marked y elevated, hydroxyurea can be used or to or in conjunction with imatin b pror to or in conjunction with imatin b

prorto cytoreduction is required because of signs of the hyperleukocytic syndrome, If rapheresis and hydroxyurea often are combined

patients with newly diagnosed chronic phase CML should be started on imatinib, patients was by mouth. Imatinib is easier to use, induces a higher frequency of 400 mg/sc, muches a higher frequency of complete cytogenetic remission, and remato ogic remission of the CML clone (molecular and cytogenetic remission). nemative suppression of the CML clone (molecular remission) than therapy with interferon (INF)-a.

The goal of imatinib therapy is to decrease the cells bearing the t (9;22) translocation The your cells) to the lowest levels possible, under which conditions normal levels possible, under which conditions normal (polyclonal) hematopoiesis is restored.

Alografting continues to play a prominent role in the treatment of patients with Supoptimal imatinib responses, who are refractory or intolerant to tyrosine kinase nhibitors, and remains the optimal therapy in those who progress to accelerated phase or b ast crisis.

. Pat ents in the chronic phase of CML who are younger than 65 years and who have an dentical twin, or a histocompatible sibling, or who are younger than 55 years with access to a histocompatible unrelated donor, can be transplanted after intensive therapy, usually with cyclophosphamide and fractionated total-body irradiation (TBI) or a combination of busulfan and cyclophosphamide. Busulfan can be administered as an intravenous preparation and as a single daily dose.

### Polycythemia Vera:

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- Povycythemia vera (PV), also called polycythemia rubra vera, is a chronic clonal mye opro iferative disorder characterized by a striking absolute increase in the number of red blood corpuscles and in the total blood volume, and usually by leukocytosis,
- The bone marrow is typically hypercellular and exhibits hyperplasia of myeloid, erythroid, and megakaryocyte lineages.
- PV usually has an insidious onset, most commonly during the sixth decade of life.
- Thrombotic episodes are the most common and the most important complications of PV, occurring in about one-third of the patients.
- Most symptoms are related to the increased red cell mass and hematocrit. Usually, there is also an increased total blood volume.
- Together, these factors cause abnormal blood flow, particularly on the low-pressure venous side of the circulation, which becomes greatly distended.
- Patients are plethoric and cyanotic due to stagnation and deoxygenation of blood in peripheral vessels. Headache, dizziness, hypertension, and gastrointestinal symptoms
- Intense pruritus and peptic ulceration may occur, both possibly resulting from the
- High cell turnover gives rise to hyperuricemia; symptomatic gout is seen in 5% to 10% of cases.



of right

Aby ist

The diagnosis of polycythaemia vera requires either all 3 major criteria or the first major criteria plus the minor criterion3.

Major criteria:

Major criteria:

E exated haemoglobin concentration (>16.5 g/dL in men; >16.0 g/dL in women) or Elevated haematocrit (>49% in men, 48% in women) or Increased red blood cell.

Elevated haematocrit (>49% in men, 48% in women) or Increased red blood cell. mass ( 25% above mean normal predicted value).

Bone marrow biops, showing age-adjusted hypercellularity with trilineage growth panmyeicsis) including prominent erythroid, granulocytic, and megakaryor it c provide at on with pieomorphic, mature megakaryocytes (differences in size)

Presence of JAK2 V617F or JAK2 exon 12 mutation.

### Minor criterion:

Subnormal serum erythropoletin level a Major criterion 2 (bone marrow biopsy) may not be required in patients with sustained absolute erythrocytosis haemoglobin concentrations of >

18.5 g/dL in men or > 16.5 g/dL in women and haematocrit values of > 55.5% in men or > 49.5% in women), if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in as many as 20% of patients) can only be detected by bone marrow biopsy, and this finding may predict a more rapid progression to overt myelofibrosis (post-PV myelofibrosis) {253}.

- PV is generally an indolent disorder, the clinical course of which is measured in decades, and its management should reflect its tempo.
- · Thrombosis due to erythrocytosis is the most significant complication, and maintenance of the hemoglobin level at <140 g/L (14 g/dL; hematocrit <45%) in men and <120 g/L (12 g/dL; hematocrit <42%) in women is mandatory to avoid thrombotic complications.
- Phlebotomy serves initially to reduce hyperviscosity by bringing the red cell mass into the normal range.
- · Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and to induce a state of iron deficiency that prevents an accelerated reexpansion of the red cell mass.
- In most PV patients, once an iron-deficient state is achieved, phiebotomy is usually only required at 3-month intervals.
- Extended survival with treatment has revealed that PCV tends to evolve to a "spent phase," during which clinical and anatomic features of primary myelofibrosis develop.
- The disease undergoes this transition in about 15% to 20% of patients after an
- It is marked by the appearance of obliterative fibrosis in the bone marrow (myelofibrosis) and extensive extramedullary hematopoiesis, principally in the



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Primary Myelofibrosis: The hallmark of primary myelofibrosis is the development of obliterative

The replacement of the marrow by fibrosis suppresses bone marrow hematopoiesis, The replacement of the replaceme

Activating JAK2 mutations are present in 50% to 60% of cases and activating MPL mutations in an additional 1% to 5% of cases.

Pathogenetic mechanisms in PMF include (a) megakaryocyte weighted clonal myeloproliferation, (b) reactive bone marrow stromal changes, and (c) extramedullary hematopoiesis (EMH).

The chief pathologic feature is the extensive deposition of collagen in the marrow by non-neoplastic fibroblasts.

The fibrosis inexorably displaces hematopoietic elements, including stem cells, from the marrow and eventually leads to marrow failure.

#### Nonmalignant Malignant Acute leukemia (lymphocytic, myelogenous, megakaryocytic) HIV infection Hyperparathyroidism (hrome myelogenous leukernia Renal osteodystrophy Ham cell leukemia Systemic lupus erythematosus Hodgkin's disease Tuberculosis ld opathic myelofibrosis Vitamin D deficiency Lymphoma Thorium dioxide exposure Mait ple myeloma Gray platelet syndrome Myelody splasia Metastatic carcinoma Polycythemia vera

Systemic mastocytosis Hepatomegaly is detectable in two-thirds of patients, and splenomegaly is present on palpation or imaging studies in almost all patients at the time of diagnosis.

### ster I in dings that disput his the pale tion

Prefibrotic stage.

Anemia may be absent or mild

Leukocytosis may be absent or slight

Thrombocythemia very frequent.

BCR-ABL fusion gene absent.

Presence of JAK2 mutation indicative of diagnosis of myeloproliferative disease.

Ce.lular marrow with mild increase in granulopoiesis; increased megakaryocytes, clusters of very dysmorphic megakaryocytes and megakaryocytic nuclei; no to very slight increase in reticular fibers on silver stain.

### 428 | PATHOLOGY

Palpable splenomegaly infrequent.

Absent or slight anisopoikilocytosis including teardrop red cells

Fully developed stage

Marrow reticulin fibrosis plus or minus collagen fibrosis

BCR-ABL fusion gene absent

JAK2 mutation in approximately 50% of patients

Splenomegaly

Anisopoikilocytosis with teardrop red cells in every oil immersion field

Immature myeloid cells in blood.

Increased CD34-positive cells in blood.

Erythroblasts in blood.

Marrow usually hypercellular but invariably has increased megakaryocytes, clusters of highly dysmorphic megakaryocytes, and megakaryocyte bare nuclei regardless of overall marrow cellularity,

### Diagnostic criteria for pre fibrotic phase of PMF:

The diagnosis of prefibrotic/early primary myelofibrosis requires that all 3 major criteria and at least 1 minor criterion are met.

### Major criteria:

- 1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade > 1a, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis.
- 2. WHO criteria for BCR-ABL1-pos\i\ve chronic myeloid leukaemia, polycythaemia vera, essential thrombocythaemia, myelodysplastic syndromes, or other myeloid neoplasms are not met.
- 3. JAK2, CALR, or MPL mutation

or

Presence of another clonal marker<sup>b</sup>

or

Absence of minor reactive bone marrow reticulin fibrosis<sup>c</sup>

### Minor criteria:

Presence of at least one of the following, confirmed in 2 consecutive determinations:

- Anaemia not attributed to a comorbid condition.
- Leukocytosis ≥11 x 109/L.
- Palpable splenomegaly.
- Lactate dehydrogenase level above the upper limit of the institutional reference

MINC

0

plagnostic criteria for overtifibrotic phase of PMF: The diagnosis of overt primary myelofibrosis requires that all 3 major criteria and at east 1 minor criterion are met

1. Megakaryocyte proliferation and atypia, accompanied by reticulin and/or Major criteria: collagen fibrosis grades 2 or 3°

2 WHO criteria for essential thrombocythaemia, polycythaemia vera, BCR-ABL1pos\i\ve chronic myeloid leukaemia, myelodysplastic syndrome, or other myeloid neoplasms 5 are not met.

3. JAK2, CALR, or MPL mutation

Presence of another clonal marker 0

Absence of reactive myelofibrosis'1

Presence of at least one of the following, confirmed in 2 consecutive determinations:

Anaemia not attributed to a comorbid condition.

\_eukocytosis ≥11 × 109/L.

Palpable splenomegaly.

Lactate dehydrogenase level above the upper limit of the institutional reference

Leukoerythroblastosis.

### **Essential Thrombocythemia:**

• Essential thrombocythemia is a clonal stem cell disorder characterized by an overproduction of plate.ets and associated with mutations in JAK2 or MPL.

· Complications include thrombosis (predominantly arterial), hemorrhage, and progression to myelofibrosis or acute myeloid leukemia.

 Diagnosis requires exclusion of reactive thrombocytosis and other myeloid malignancies associated with a raised platelet count.

Therapy is aimed at reducing thrombotic complications and includes modification of known cardiovascular risk factors and antiplatelet therapy for the majority of patients.

 Those at high risk of thrombosis are also considered for cytoreductive therapy with agents such as hydroxyurea, anagrelide, or interferon-a. Although survival in the first decade following diagnosis appears similar to controls, mortality rates increase thereafter as a consequence of disease complicaions.

The most frequent symptom complex (~30% prevalence rate) is recognized as "microvascular symptoms" consisting of headaches, visual symptoms, lightheadedness, atypical chest pain, acral dysesthesia, and erythromelalgia. Among these symptoms, erythromelalgia is the most impressive but least prevalent, occuring in <5% of patients.

Erythromelalgia is characterized by painful erythematous discoloration of the feet and/or hands that results from abnormal platelet-endothelium interaction.

	de la	idal Throndrony the said
Age Group	First Line	Second Line
<40 years old	Interferon-	Hydroxyurea
		Anagrelide
40-75 years	Hydroxyurea	Interferon-
		Anagrehde
>75 years	Hydroxyurea	Anagrelide
		Pipobroman
		Busulphan
		Radioactive phosphorus

### Diagnostic criteria for ET:

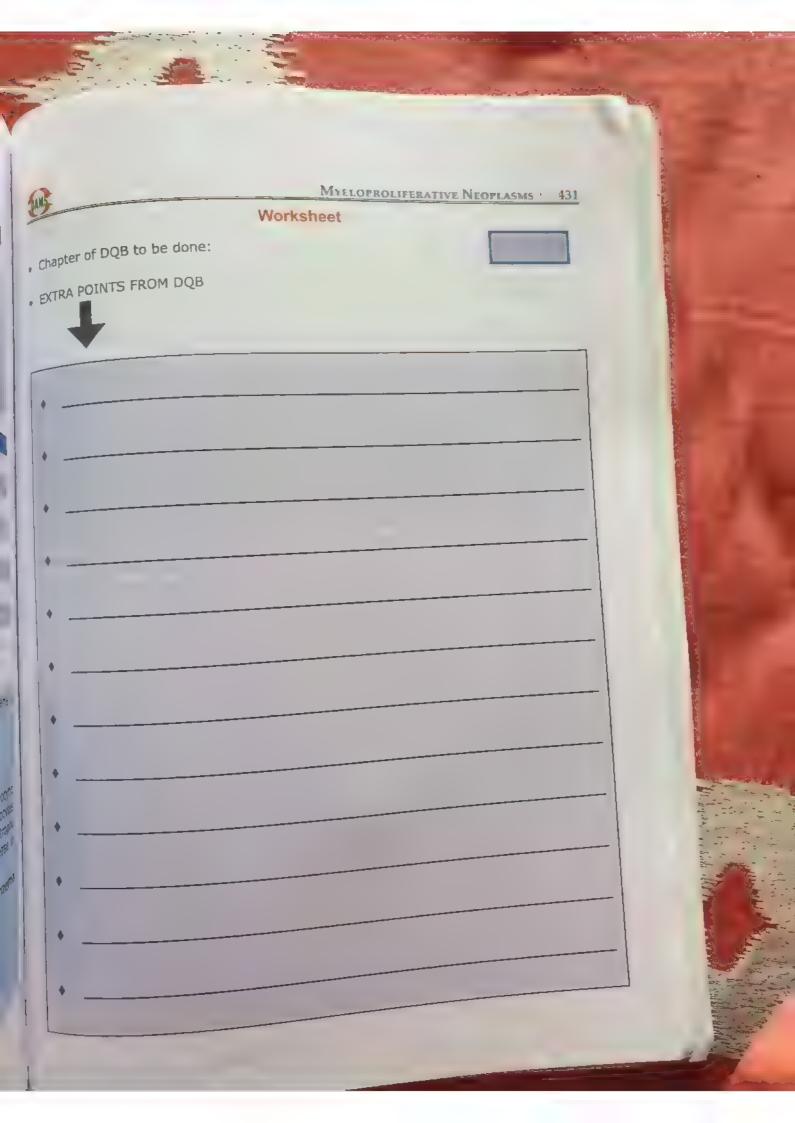
The diagnosis of essential thrombocythaemia requires that either all major criteria or the first 3 major criteria plus the minor criterion are met.

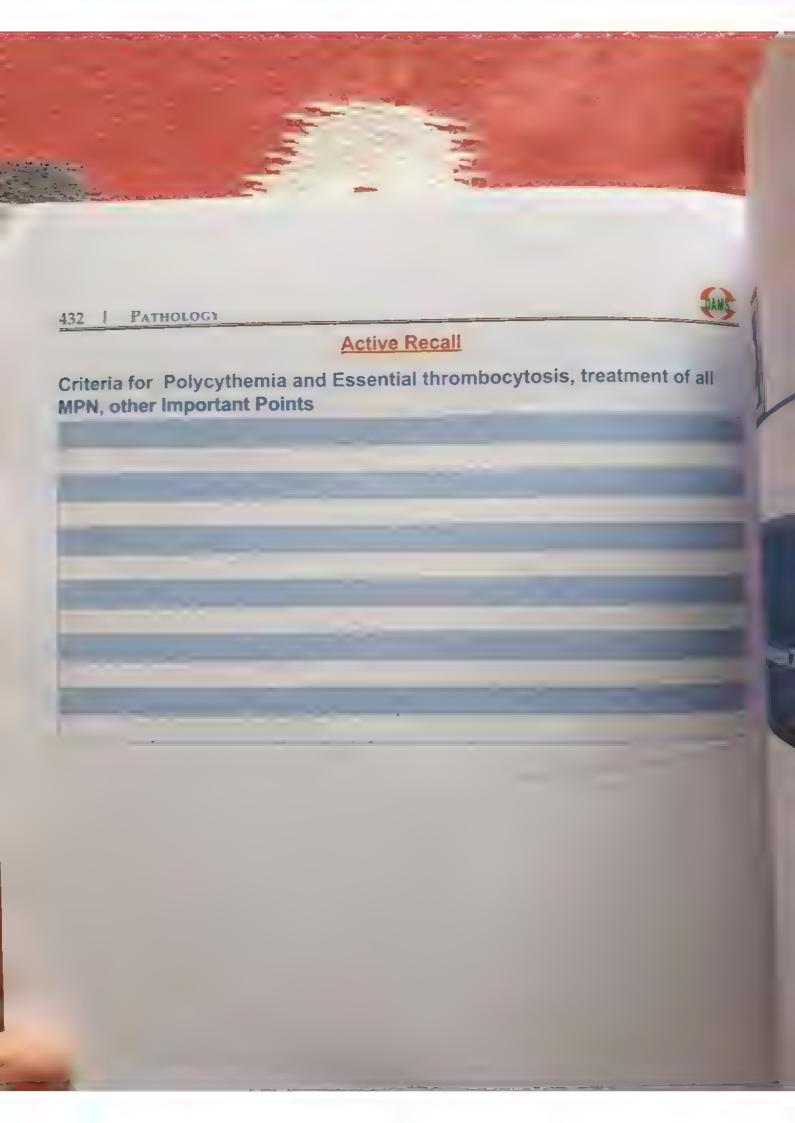
### Major criteria:

- 1. Platelet counts ≥450 x 109/L.
- 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophi granulopoiesis or erythropoiesis; very rarely a minor (grade 1a) increase in reticulin fibres.
- 3. WHO criteria for BCR-ABL1-positive chronic myeloid leukaemia, polycythaemia vera, primary myelofibrosis, or other myeloid neoplasms are not met.
- 4. JAK2, CALR, or MPL mutation.

### **Minor criterion:**

Presence of a clonal marker or Absence of evidence of reactive thrombocytosis.







# PLATELET AND COAGULATION DISORDERS

# CONCEPTS

Ecocept 22.1 | Platelet and Coagulation Disorders



## Concept 22 1: Platelet and Coagulation Disorders

Concept 22 1: Platelet and Coagulation, platelet disorders, coagulation Learning Objectives: Physiology of coagulation, platelet disorders, coagulation disorders, DIC, treatment and how to differentiate these diseases from each other

### Time Needed

I reading	120 mm
2 <sup>nd</sup> reading	60 mm

	2 <sup>nd</sup> read	ing 60 min
C		olification of District and Removalish
Major Ty	pes , Disorders	Examples
Nequired	Thrombocytopenias	Autoimmune and alloimmune, drug-induced, hypersplenism hypoplastic (primary, myelosuppressive therapy, myelophthism marrow infiltration), disseminated intravascular coaggistion (DIC), thrombotic thrombocytopenic purpura, hemolyticuremic syndrome.
	Liver diseases	Cirrhosis, acute hepatic failure, liver transplantation thrombopoietin deficiency.
	Renal failure	
	Vitamin K deficiency	Malabsorption syndrome, hemorrhagic disease of the newborr prolonged antibiotic therapy, malnutrition, prolonged bihary obstruction.
	Hematologic disorders	Acute leukemias (particularly promyelocytic), myelody splasia monoclonal gammopathies, essential thrombocythemia.
rited Do	Acquired antibodies against coagulation factors.	Neutralizing antibodies against factors V, VIII, and XIII, accelerated clearance of antibody-factor complexes, e.g., acquired von Willebrand disease, hypoprothrombinemia associated with antiphospholipid antibodies
	DIC	and chronic (malignancies, trauma, obstetric complications, products of conception).
	Drugs Vascular	Antiplatelet agents, anticoagulants, antithrombins, and thrombolytic, hepatotoxic, and nephrotoxic agents.
	Deficiencies of	Nonpalpable purpura ("semle," solar, and factitious purpura), use of corticosteroids, vitamin C deficiency, ch.ld abuse, thromboembolic, purpura fulminans, palpable purpura (Henoch-Schönlein, vasculitis, dysproteinemias, amyloidosis, Hemophilia A (factor VIII.).
	coagulation factors	deficiency), deficiency, afficiency), hemophilia B (factor I)
	Platelet disorders	and XIII and von Willebrand disease  Glanzmann thrombasthenia, Bernard-Soulier syndrome, platele granule disorders.
	Fibrinolytic disorders	α2-Antiplasmin deficiency, plasminogen activator inhibitor-l
	Vascular	Hemorrhagic telangiectasias
d	Connective tissue isorders	Ehlers-Danios syndrome

Fig. 22.1

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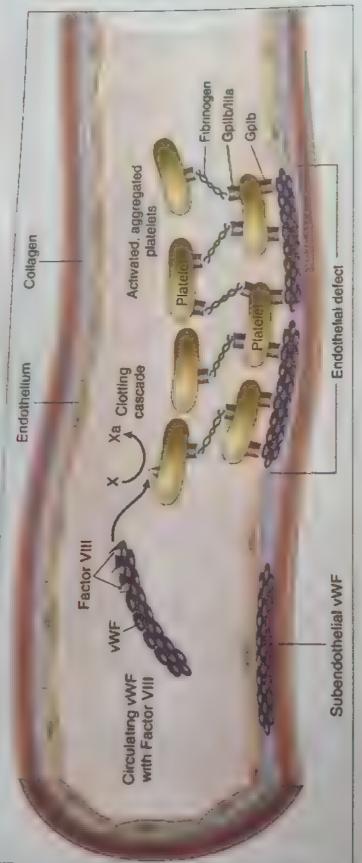
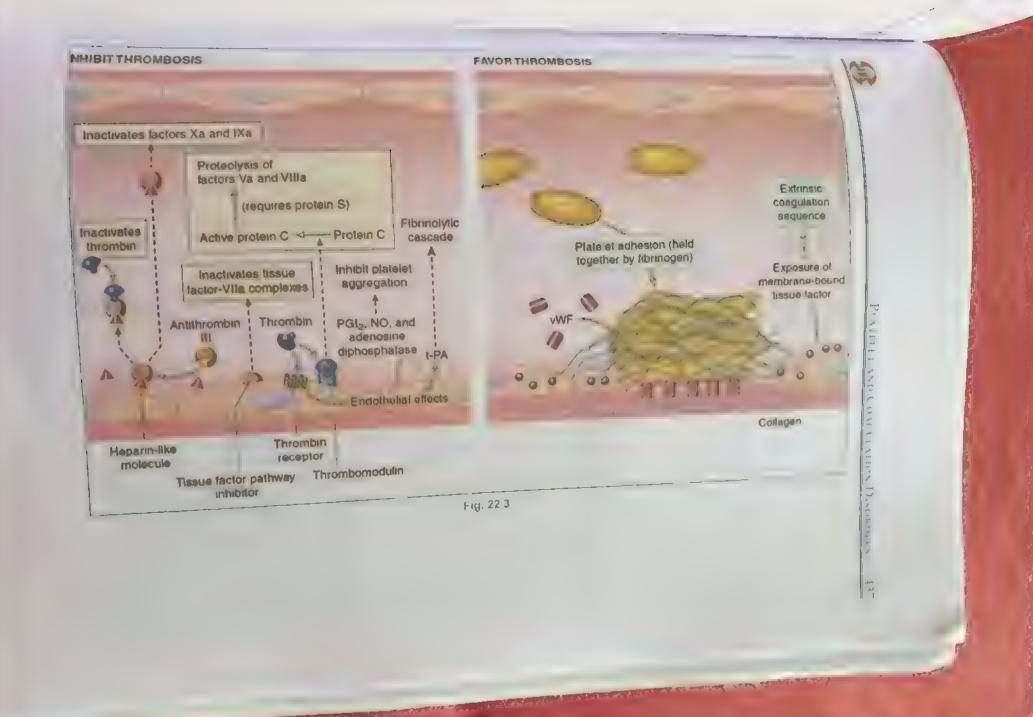
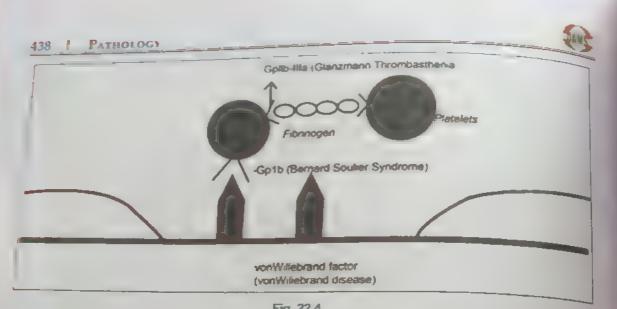


Fig. 22.2





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Fig. 22.4

The vitamin K-dependent factors group includes coagulation factors II, VII, IX, and X However, it is important to remember that the anticoagulant proteins S, C, and Z are also vitamin K-dependent. Each of these proteins contains a number of glutamic acid residues at its amino terminus that are y-carboxylated by a vitamin K-dependent mechanism. This results in a novel amino acid, y-carboxyglutamic acid, which is important in promoting a conformational change in the protein that promotes binding of the factor to phospholipid. Because this binding is crucial for coordinating the interaction of the various factors, the proteins produced in the absence of vitamin K (PIVKAs) that are not y-carboxylated are essentially functionless. The vitamin K-dependent factors are proenzymes or zymogens, which require cleavage sometimes with release of a small peptide (activation peptide) to become functional. Measurement of these activation peptides has been used as a means of assessing coagulation activation

Factors VIII and V are the two most labile of the coagulation factors, and they are rapidly lost from stored blood or heated plasma. They share considerable structural homology and are cofactors for the serine proteases FIX and FX, respectively; they both require proteolytic activation by factor IIa or Xa to function. Factor VIII circulates in combination with VWF, which is present in the form of large multimers of a basic 200 kD monomer. One function of VWF is to stabilize factor VIII and protect it from degradation. In the absence of VWF the survival of factor VIII in the circulation is extremely short (i.e., <2 hours instead of the normal 8–12 hours). VWF may also serve to deliver factor VIII to platelets adherent to a site of vascular injury. Once factor VIII has been cleaved and activated by thrombin it no longer binds to VWF. **Prothrombin Time:** 

The PT test measures the clotting time of plasma in the presence of an optimal concentration of tissue extract (thromboplastin) and indicates the overall efficiency of the extrinsic clotting system. Although originally thought to measure prothrombin, the test is now known to depend also on reactions with factors V, VII, and X and on the fibrinogen concentration of the plasma.

# The common causes of prolonged one-stage PTs are as follows:

Administration of oral anticoagulant drugs (vitamin K antagonists).

- Liver disease, particularly obstructive.
- Vitamin K deficiency.
- Disseminated intravascular coagulation
- Rarely, a previously undiagnosed factor VII X V or prothrombir deficiency or defect Note With garety. The prothrombin, factor X, or factor V deficiency the APTT will also be prolonged.

# **Activated Partial Thromboplastin Time:**

The test measures the clotting time of plasma after the activation of contact factors but without added t ssue thromboplastin and so indicates the overall efficiency of the ntrinsic pathway.

# The common causes of a prolonged APTT are as follows:

Disseminated intravascular coagulation.

. Liver disease

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- Mossac translusion with plasma-depleted red blood cells.
- Administration of or contamination with heparin or other anticoagulants.
- Vercalating anticoagulant (inhibitor).
- Deficiency of a coagulation factor other than factor VII.

The APTT is also moderately prolonged in patients taking oral anticoagulant drugs and n the presence of vitamin K deficiency. Occasionally, a patient with previously undiagnosed haemophilia or another congenital coagulation disorder presents with an isolated prolonged APTT.

# The common causes of prolonged TT are as follows:

- Hypofibrinogenaemia as found in DIC and, more rarely, in a congenital defect or deficiency.
- Raised concentrations of LDP, as encountered in DIC or liver disease.
- Extreme prolengation of the TT is nearly always a result of the presence of heparin, which interferes will the thrombin fibrinogen reaction. If the presence of heparm is suspected, a Reptilase time test should be carried out (see p. 407). Low molecular weight heparin (LMWH) produces only a slight prolongat on at therapeutic levels
- Dysfibranogenaemia, either inherited or acquired, in liver disease or in neonates.
- Hypoalbuminaemia.



### Shortening of the TT occurs in conditions of coagulation activation.

Finding	Disorders of Coagulation	Disorders of Platelets or Vessels
Petechiae	Rare	Characteristic
Deep dissecting hematomas	Characteristic	Rare
Superficial ecchymoses	Common; usually large and solitary	Characteristic; usually small and multiple
Hemarthrosis	Characteristic	Rare
Delayed bleeding	Common	Rare
Bleeding from superficial cuts and scratches	Mınimal	Persistent; often profuse
Sex of patient	80-90% of inherited forms occur only in male patients.	Relatively more common in females.
Positive family history	Common	Rare (except von Willebrand disease and hereditary hemorrhagic telangiectasia).

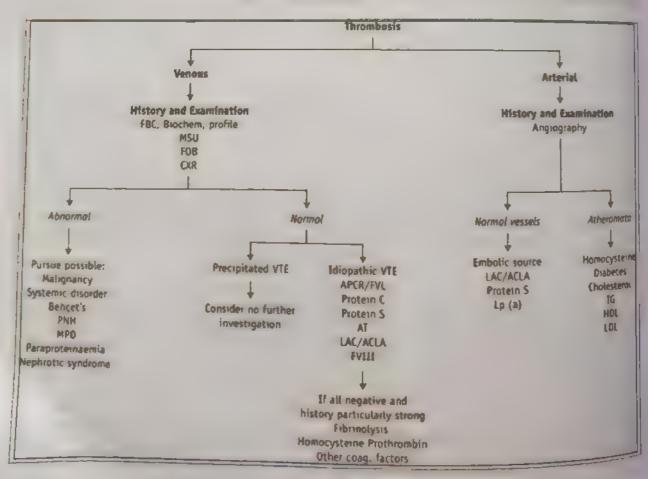


Fig. 22.5

it we thrown breeding

cohalhematomas in newborns, hemarthroses, Lephanicia, and intramuscular, intracerebral, and groperitoneal hemorrhages

muy-related bleeding and mild spontaneous bleeding.

Bleeding from stump of umbilical cord and habitual abortions

impaired wound healing.

Facial purpura in newborns.

Recurrent severe epistaxis and chronic iron deficiency anemia.

Thrombocytopenias, platelet dysfunction, von Willebrand disease.

Severe hemophilias A and B, severe deficiencies of factor VII, X, or XIII, severe type 3 von Willebrand disease, afibrinogenemia.

Mild and moderate hemophilias A and B, severe factor XI deficiency, moderate deficiencies of fibrinogen and factors II, V, VII, or X, combined factors V and VIII deficiency, 2-antiplasmin deficiency

Afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, factor XIII deficiency.

Factor XIII deficiency.

Glanzmann thrombasthenia, severe thrombocytopenia.

Hereditary hemorrhagic telangiectasias.

#### d Production:

Decreased Production:			Accelerated	Pooling
Measurement	Hypoproliferation or Hypoplasia	Ineffective Thrombopoiesis <sup>b</sup>	Destruction <sup>c</sup>	Abnormal
		Increased	M increased	V increased
Total megakaryocyte mass <sup>a</sup>	Decreased	M increased	Increased	V increased
Megakaryocyte number	Decreased		Increased	Vincreased
Megakaryocyte volume	Increased	Normal or V decreased	Hierensea	
Platelet turnover rate or	Decreased	Decreased	Increased	V increased
production rates		Decreased	Decreased	? Normal
Total platelet mass	Decreased		Decreased	Increased
Splenic platelet pool	Decreased	Decreased	-	V shortened
Platelet our viscol	Normal	V shortened	Shortened	4 3110110110

M markedly, V, variably,

Platelet survival

Mainly in megaloblastic hematopoiesis; component of accelerated destruction present in some cases.

M nor component of meffective thrombopotesis present in some cases.

Normal

Equated to total thrombopoiesis

I stated to effective thrombopotesis.

\*\* representative of sequestered antibody-sensitized platelets.



### Artifactual thromboextopenia:

the entry of the plant-dependent managed by appeals are the operation Platelet satellitism Grant platelets

### Decreased platelet production:

Hypoplasia of megakaryocytes

Ineffective thrombopotesis

Disorders of thrombopoietic control

Hereditary thrombocytopenias

### Increased platelet destruction:

Caused by immunologic processes

Autoimmune

Idiopathic

Secondary: Infections, pregnancy, collagen vascular disorders, lymphoproliferative disorders, drugs, miscellaneous.

Alloimmune

Neonatal thrombocytopenia

Posttransfusion purpura

Caused by nonimmunologic processes

Thrombotic microangiopathies

Dissemmated intravascular coagulation

Thrombotic thrombocytopenic purpura

Hemolytic-uremic syndrome

Platelet damage by abnormal vascular surfaces

Miscellaneous

Infection

Massive blood transfusions

### Abnormal platelet distribution or pooling

Disorders of the spleen (neoplastic, congestive, infiltrative, infectious, of unknown cause) Hypothermia.

Dilution of platelets with massive transfusions.

A count below 100,000 platelets µL is generally considered to constitute thrombucytopenia

However, spontaneous bleeding does not become evident until platelet counts fall below 20,000 plateiers. μL.

Platelet counts in the range of 20,000 to 50,000 platelets/µL can aggravate post-traumatic bleeding. Bleeding resulting from thrombocytopenia is associated with a normal PT and PTT.

Primary

- A. Idiopathic autoimmune thrombocytopenic purpura.
- 2. Secondary
  - A. Autoimmune diseases: systemic lupus erythematosus, antipnospholipid syndrome, autoimmune thyroiditis
  - B Lymphoproliterative disorders etironic lymphocytic leukemia. Hodgkin lymphoma, large granular lymphocytic leukemia
  - C. Infections: HIV, hepatitis C, Helicobacter pylori .
  - D. Myelodysplastic syndrome.
  - L Agammaglobulinemia, hypogammaglobulinemia, immunogiobulin A deficiency
  - F Drugs quinidine, gold, heparin, penicillin, procainamide, α-methyldopa, sulfamethoxazole

Feature	Acute ITP	Chronic IIP
eak age of incidence	Children, 2 6 yr	Adults, 20–40 yr
Sex predilection	None	3 1 female to male
Artecedent infection	Common 1 3 wk before	L nusual
	Abrupt	Insidious
Onset of bleeding	Present in severe cases	Usually absent
Her orr ag.c ballae in mouth	- 20,000 μl	30,000-80,000 µl
Pratelet count	Common	Rare
Emphil a and lymphocytosis	2 -6 wk, rarely longer	Months or years
Duration		Uncommon
Sportaneous remissions	Occur in 80% of cases	embrane glycoprote

The autoantibodies, most often directed against platelet membrane glycoproteins IIb-IIIa or Ib-IX, can be demonstrated in the plasma and bound to the platelet surface in about 80% of patients. In the overwhelming majority of cases, the antiplatelet antibodies are of the IoG class.

Thrombocytopenia is defined as a blood platelet count less than 150 \(\xi\) 109/L. The blood film usually demonstrates isolated thrombocytopenia without erythrocyte or leukocyte abnormalities. Platelet anisocytosis is a common finding in ITP. Mean platelet volume abnormalities. Platelet anisocytosis is a common finding in ITP. Mean platelet volume abnormalities and platelet distribution width are increased. Platelets may be abnormally large or abnormally small. The former reflect accelerated platelet production and the latter abnormally small. The former reflect destruction.

Almost all patients respond to glucocorticoids (which inhibit phagocyte function), but many eventually relapse. In such individuals, splenectomy normalizes the platelet count in about two thirds of patients, but with the attendant in-creased risk of bacterial sepsis. In about two thirds of patients, but with the attendant in-creased risk of patients, but with the attendant in-creased risk of bacterial sepsis. Immunomodulatory agents such as intravenous immunoglobulin or anti-CD20 antibody.

OX

(ntuximab) are often effective in patients who relapse after so enectomy or for whom splenectomy is contraindicated.

### Heparin Induced Thrombocytopenia:

Heparin-induced thrombocytopenia (HIT) has a distinctive pathogenesis and is of particular importance because of its potential for severe clinical consequences Thrompocytopenia occurs in about 5% of persons receiving heparin

- Most develop so-called type I thrombocytopen a, which occurs rap div after the Most develop so-called type I thrombot, or the onset of therapy and is of little clinical importance, sometimes resolving despite the
- continuation of therapy.
- It most likely results from a direct platelet-aggregating effect of heparin.
- Type II thrombocytopenia is less common but of much greater clinical significance It occurs 5 to 14 days after therapy begins (or sooner if the person has been sensitized
- to heparin) and, paradoxically, often leads to life-threatening venous and artera thrombosis.
- This severe form of HIT is caused by antibodies that recognize complexes of neparin and platelet factor 4, which is a normal component of platelet granules.
- Binding of antibody to these complexes activates platelets and promotes thrombosis, even in the setting of thrombocytopenia.
- Unless therapy is immediately discontinued and an alternative nonhepann anticoagulant instituted, clots within large arteries may lead to vascular insufficiency and limb loss, and emboli from deep venous thrombosis can cause fatal pulmonary thromboembolism.
- The risk of severe HIT is lowered, but not completely eliminated, by the use of lowmolecular-weight heparin preparations.
- Unfortunately, once severe HIT develops even low-molecular-weight hepanns exacerbate the thrombotic tendency and must be avoided.

### Thrombotic Thrombocytopenic Purpura:

Thrombotic Microangiopathies: Causes and Associations.

Hickory, better thromasservice performance Purpura

Deficiency of ADAMTS13

Inherited

Acquired (autoantibodies)

Hemolytic Uremic Syndrome

Epidemic: Escherichia coli strain O157: H7 infection

Endothelial damage by Shiga-like toxin

Nonepidemic: alternative complement pathway inhibitor deficiencies (complement factor H, membrane cofactor protein (CD46), or factor 1)

Inherited

Acquired (autoantibodies).

Miscellaneous associations

Drugs (cyclosporine, chemotherapeutic agents).

Radiation, bone marrow transplantation.

Other infections (HIV, pneumococcal sepsis).

Conditions associated with autoimmunity (systemic lupus erythematosus, HIV infection, lymphoid

TTP IS an important diagnosis to consider in any patient presenting with Tro is an and microangiopathic hemolytic anemia, since delays in diagnos s thrombocytopenia and microangiopathic hemolytic anemia, since delays in diagnos s thrombucyto. With plasma exchange, which removes autoantibodies and provides can be fatal. With plasma exchange, which removes autoantibodies and provides can be raid ADAMTS13, TTP (which once was uniformly fatal) can be treated successfully functional 80% of patients. in more than 80% of patients.

In contrast, HUS is associated with normal levels of ADAMTS13 and is initiated by

several other distinct defects Epidemic, "typical" HUS is strongly associated with infectious gastroenteritis Epidenie, caused by Escherichia coli strain O157:H7, which elaborates a Shiga-like

This toxin is absorbed from the inflamed gastrointestinal mucosa into the circulation, where it alters endothelial cell function in some manner that results in plateiet

activation and aggregation.

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, Children and the elderly are at highest risk.

Those affected present with bloody diarrhea, and a few days later HUS makes its appearance. With appropriate supportive care complete recovery is possible, but irreversible renal damage and death can occur in more severe cases.

, Nonepidemic, "atypical" HUS is often associated with defects in complement factor H, membrane cofactor protein (CD46), or factor I, three proteins that normally act to prevent excessive activation of the alternative complement

Defic encies of these proteins can be caused by inherited defects or acquired inhibitory

autoantibodies and are associated with a remitting, relapsing course.

 Unlike TTP, the basis for the platelet activation in HUS is unclear; presumably, both Sn ga-like toxin produced by pathogenic E. coli and defects in complement-regulatory proteins after endothelial cell function in some way that promotes platelet activation.

Inherited disorders of platelet function can be classified into three pathogenically distinct groups: (1) defects of adhesion, (2) defects of aggregation, and (3) disorders of platelet secretion (release reaction).

- Bleeding resulting from defective adhesion of platelets to subendothelial matrix is best Ilustrated by the autosomal recessive disorder Bernard-Soulier syndrome, which is caused by an inherited deficiency of the platelet membrane glycoprotein complex Ib-IX. This glycoprotein is a receptor for vWF and is essential for normal platelet adhesion to the subendothelial extracellular matrix.
- Bleeding due to defective platelet aggregation is exemplified by Glanzmann thrombasthenia, which is also transmitted as an autosomal recessive trait. Thrombasthenic platelets fail to aggregate in response to adenosine diphosphate (ADP), collagen, epinephrine, or thrombin because of deficiency or dysfunction of glycoprotein IIb-IIIa, an integrin that participates in "bridge formation" between

 Disorders of platelet secretion are characterized by the defective release of certain mediators of platelet activation, such as thromboxanes and granule-bound ADP.

Among the acquired defects of platelet function, two are clinically significant.

 The first is caused by ingestion of aspirin and other nonsteroidal anti-inflammatory drugs. Aspirin is a potent, irreversible inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A2 and prostaglandins These mediators



#### 146 PATHOLOGY

montant roles in platelet aggregation and subsequent release reactions The intip ate et effects of aspir n form the basis for its use in the prophylaxis of coronary the mbess

cremit is the second condition exemplifying an acquired defect in platelet function The pathodeness of pratelet dysfunction in uremia is complex and involves defects in agnes on granule secretion, and aggregation

### 15 malities of Glycoprotein Adhesion Receptors

- 1. (Glycoprotein IIb/Illa, CD41/CD61): Glanzmann thrombasthema
- B Utycoproteins Ib (CD42b,c)/IX(CD42a)/V: Bernard-Soulier syndrome
- C. Glycoprotein GPIb (CD42b): platelet-type (pseudo-) von Willebrand disease
- D. Glycoprotein Ia/IIa; very late antigen [VLA]-2; CD49b/CD29).
- E. CD36 (Glycoprotein IV).
- F. Glycoprotein VI.
- II. Abnormalities of Platelet Granules.
  - A. Alpha-Storage pool deficiency
  - B. Gray platelet syndrome (alpha-storage pool deficiency).
  - C. Storage pool deficiency.
  - D. Quebec platelet disorder.
- III. Abnormalities of Platelet Coagulant Activity (Scott syndrome).
- IV. Abnormalities of Platelet Signaling and Secretion.
- Abnormanties of a Cytoskeletal Structural Protein beta! Jubulin
- VI. Abnormalities in Cytoskeletal Linking Proteins.
  - A. Wiskott-Aldrich syndrome protein (WASP)
  - B Kindhn-3 Leukocyte adhesion defect-III (LAD-III); LAD-1 variant, integrin activation deficiency
- VII Abnormalities of Transcription Factors Leading to Functional Defects.
  - A RUNXI (familial platelet dysfunction with predisposition to acute myelogenous leukemia).

  - C FHH (d morphic dysmorphic platelets with grant alpha granules and thrombocytopenia, Pans-

## Wiskott Aldrich Syndrome:

- Wiskott-Aldrich syndrome is an X-linked recessive disease characterized
   by thromboeytoponia by thrombocytopenia, eczema, and a marked vulnerability to recurrent
- The thymus is morphologically normal, at least early in the course of the disease, but there is progressive secondarional, at least early in the course of the disease, but there is progressive secondary depletion of T lymphocytes in the peripheral blood

and in the T-cell zones (paracortical areas) of the lymph nodes, with variable loss of cellular immunity.

- patients do not make antibodies to polysaccharide antigens, and the response to protein antigens is poor. IgM levels in the serum are low, but levels of IgG are usually normal.
- paradoxically the levels of IgA and IgE are often elevated. Patients are also prone to developing non-Hodgkin B-cell lymphomas
- . The Wiskott-Aldrich syndrome is caused by mutations in the gene encoding Wiskott-Aldrich syndrome protein (WASP), which is located at Xp11.23.
- . This protein belongs to a family of proteins that are believed to link membrane receptors, such as antigen receptors, to cytoskeletal elements.
- . The WASP protein may be involved in cytoskeleton-dependent responses, including cell migration and signal transduction, but the essential functions of this protein in lymphocytes and platelets are unclear. The only treatment is bone marrow transplantation.

#### X-linked recessive traits

Hemophilia A

Hemophilia B (i. e., CRM+ and CRM- variants; hemophilia Bm, B Leyden, etc.)

#### Autosomal recessive traits

Factor XI deficiency

Prothrombin deficiency

Factor V deficiency

Factor VII deficiency

Factor X deficiency (i.e., Prower variant, Stuart variant, Friuli variant, others)

Afibrinogenemia

Hypofibrinogenemia

Factor XII deficiency

Factor XIII deficiency

#### Autosomal dominant traits:

von Willebrand disease

Dysfibrinogenemias

### Combined abnormalities:

Associated with factor VIII deficiency (i.e., factor V deficiency, hemophilia B, factor XI deficiency, factor

VII deficiency, von Willebrand disease, dysfibrinogenemias, platelet dysfunction)

Involving vitamin K-dependent factors (i.e., factors II, VII, IX, and X; factors IX and XII; others).

### Miscellaneous:

Prekallikrein deficiency

High-molecular-weight kininggen deficiency

Deficiency of physiologic inhibitors (i.e., a2-antiplasmin, abnormal a1-antitrypsin [antithrombin

Pittsburgh])

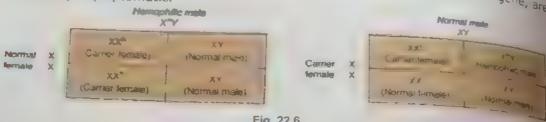
CRM, cross reacting material

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### Haemophilia:

- Hemophilia is an X-linked recessive hemorrhagic disease due to mutations in the F8 gene (hemophilia A or classic hemophilia) or F9 gene (hemophilia B).
- The disease affects 1 in 10,000 males worldwide, in all ethnic groups; hemophilia A
- Maie subjects are clinically affected; women, who carry a single mutated gene, are



- More than 500 different mutations have been identified in the F8 or F9 genes of patients with hemophilia A or B, respectively.
- One of the most common hemophilia A mutations results from an inversion of the intron 22 sequence, and it is present in 40% of cases of severe hemophilia A.
- Hemophilia A is the most common hereditary disease associated with life-
- Clinically, hemophilia A and hemophilia B are indistinguishable.
- The disease phenotype correlates with the residual activity of FVIII or FIX and can be classified as severe (<1%), moderate (1–5%), or mild (6–30%). In the severe and moderate forms, the disease is characterized by bleeding into the joints (hemarthrosis), soft tissues, and muscles after minor trauma or even spontaneous y.

		arter minor trauma or even spontaneous
Severe	≤1% of normal (≤0.01 U/mL)	Spontaneous hemorrhage from early infancy
Moderate	1 5% of normal (0.01-0.05 U/mL)	<ol><li>Frequent spontaneous hemarthroses and othe hemorrhages, requiring clotting factor replacement</li></ol>
Mıld	6-30% of normal (0.06 0.30 U/mL)	Hemorrhage secondary to trauma or surgery     Occasional spontaneous hemarthroses
Typically.	the global tocto as	Hemorrhage secondary to trauma or surgery     Rare spontaneous hemorrhage

- Typically, the global tests of coagulation show only an isolated prolongation of the aPTT assay. Patients with hemophilia have normal bleeding times and platelet counts.
- The diagnosis is made after specific determination of FVIII or FIX clotting activity.
- Factor replacement therapy for hemophilia can be provided either in response to a bleeding episode or as a prophylactic treatment.
- Primary prophylaxis is defined as a strategy for maintaining the missing clotting factor at levels 1% or higher on a regular basis in order to prevent bleeds, especially the onset of hemarthroses.



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6-30%

Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/ week) can reach puberty without detectable joint abnormalities.

### Von Willebrand Disease:

- Von Willebrand disease is the most common inherited bleeding disorder of
- The most common symptoms are spontaneous bleeding from mucous membranes (e.g., epistaxis); excessive bleeding from wounds; menorrhagia; and a prolonged bleeding time in the presence of a normal platelet count. It is usually transmitted as an autosomal dominant disorder, but rare autosomal recessive variants have been described.
- VWD is associated with either quantitative deficiency (type 1 and type 3) or qualitative abnormalities of VWF (type 2).
- The uncommon type 3 variant is the most severe form of VWD and is characterized by very low or undetectable levels of VWF, a severe bleeding diathesis, and a generally autosomal recessive pattern of inheritance.
- Type 1 VWD, the most common variant, is characterized by VWF that is normal in structure and function but decreased in quantity (in the range of 20-50% of normal).
- In type 2 VWD, the VWF is abnormal in structure and/or function.
- Type 2A VWD is associated with selective loss of the largest and most functionally active VWF multimers.
- Type 2A is further subdivided into group 1, as a result of mutations that interfere with biosynthesis and secretion, and group 2, in which the mutant VWF exhibits an increased sensitivity to proteolysis in plasma.
- Type 2B VWD is caused by mutations clustered within the VWF A1 domain, in a segment critical for binding to the platelet glycoprotein Ib (GPIb) receptor.
- These mutations produce a "gain of function" resulting in spontaneous VWF binding to platelets and clearance of the resulting platelet complexes, leading to thrombocytopenia and loss of the most active (large) VWF multimers.
- Type 2N VWD is characterized by mutations within the factor VIII binding domain of VWF, leading to disproportionately decreased factor VIII and a disorder resembling mild hemophilia A, but with autosomal recessive inheritance.
- Type 1 VWD can often be effectively managed by treatment with desmopressin (DDAVP), which transiently produces a two- to threefold increase in plasma VWF
- Response to DDAVP is generally poor in type 3 and some type 2 VWD variants.
- These disorders often require treatment with factor replacement in the form of factor VIII concentrates containing large quantities of intact VWF multimers.
- Patients with von Willebrand disease have defects in platelet function despite a normal platelet count.
- The plasma level of active vWF, measured as the ristocetin cofactor activity, is reduced.
- Because vWF stabilizes factor VIII, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. This may be reflected by a prolongation of the PTT in von Willebrand disease types 1 and 3.
- However, except in rare type 3 patients, adverse complications typical of severe factor VIII deficiency, such as bleeding into the joints, are not seen.



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Disseminated intravascular coagulation:

Disseminated intravascular coagulation (DIC) is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanisms.

blood protease activity that overcomes the	Control of the Contro
Common Chinical Universal Universal	alogic disorders
Sepsis	Immunologic disorders
Bacterial: Staphylococci, streptococci, pneumococci,	Acute hemolytic transfusion reaction
meningococci, gram-negative bacilli	Organ of fissue transplant rejection
Viral	Graft-versus-host disease
Mycotic	
Parasitic	
Rickettsial	
Trauma and tissue injury	Drugs
Brain injury (gunshot)	Fibrinolytic agents
Extensive burns	Aprotinin
Fat embolism	Warfarin (especially in neonates with protein (
Rhabdomyolysis	deficiency)
	Prothrombin complex concentrates
	Recreational drugs (amphetamines)
Vascular disorders	Envenomation
Giant hemangiomas (Kasabach-Merritt syndrome)	Snake
Large vessel aneurysms (e.g., aorta)	Insects
Obstetrical complications	Liver disease
Abruptio placentae	Fulminant hepatic failure
Amntotic-fluid embolism	Cirrhosis
Dead fetus syndrome	Fatty liver of pregnancy
Septic abortion	1 and it of pregnancy
Cancer	Miscellaneous
Adenocarcinoma (prostate, pancreas, etc.)	
demotal animal 1	Shock
eukemia) (acute promyelocytic	Respiratory distress syndrome
	Massive transfission



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### DISSEMINATED INTRAVASCULAR COAGULATION ALGORITHM

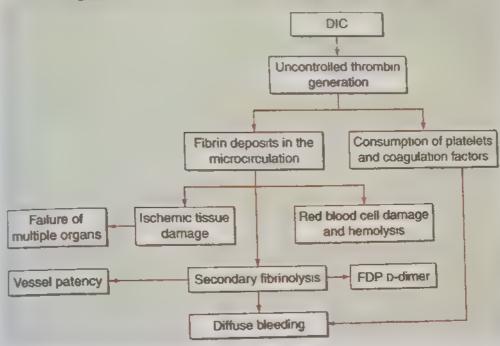


Fig. 22.7

- Two major mechanisms trigger DIC: (1) release of tissue factor or thromboplastic substances into the circulation, and (2) widespread injury to the endothelial cells.
- Common findings include the prolongation of PT and/or aPTT; platelet counts <100,000/µL3, or a rapid decline in platelet numbers; the presence of schistocytes (fragmented red cells) in the blood smear; and elevated levels of FDP.
- The most sensitive test for DIC is the FDP level. DIC is an unlikely diagnosis in the presence of normal levels of FDP.
- The D-dimer test is more specific for detection of fibrin—but not fibrinogen degradation products and indicates that the cross-linked fibrin has been digested by
- Because fibrinogen has a prolonged half-life, plasma levels diminish acutely only in severe cases of DIC. High-grade DIC is also associated with levels of antithrombin III or plasminogen activity <60% of normal.
- It is almost impossible to detail all the potential clinical presentations, but a few common patterns are worthy of description.
- These include microangiopathic hemolytic anemia; dyspnea, cyanosis, and respiratory failure; convulsions and coma; oliguria and acute renal failure; and sudden or progressive circulatory failure and shock.
- In general, acute DIC, associated with obstetric complications or major trauma, for example, is dominated by a bleeding diathesis, whereas chronic DIC, such as occurs In cancer patients, tends to present with thrombotic complications.

### Congulation Disorders and Hemost in Liver Disease

Bleeding

Portal hypertension

Esophageal vances

Thrombocytopenia

Splenomegaly

Chronic or acute DIC

Decreased synthesis of clotting factors

Hepatocyte failure

Vitamin K deficiency

Systemic fibrinolysis

DIC

Dysfibrinogenemia

Thrombosis

Decreased synthesis of coagulation inhibitors: protein C, protein S, antithrombin

Hepatocyte failure

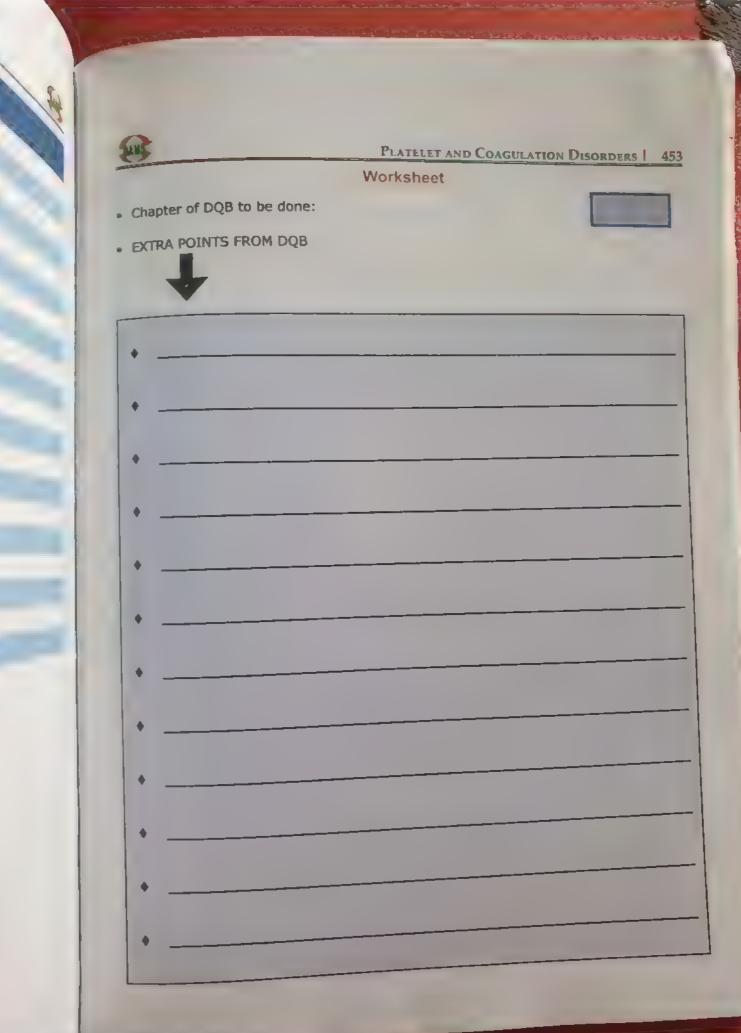
Vitamin K deficiency (protein C, protein S)

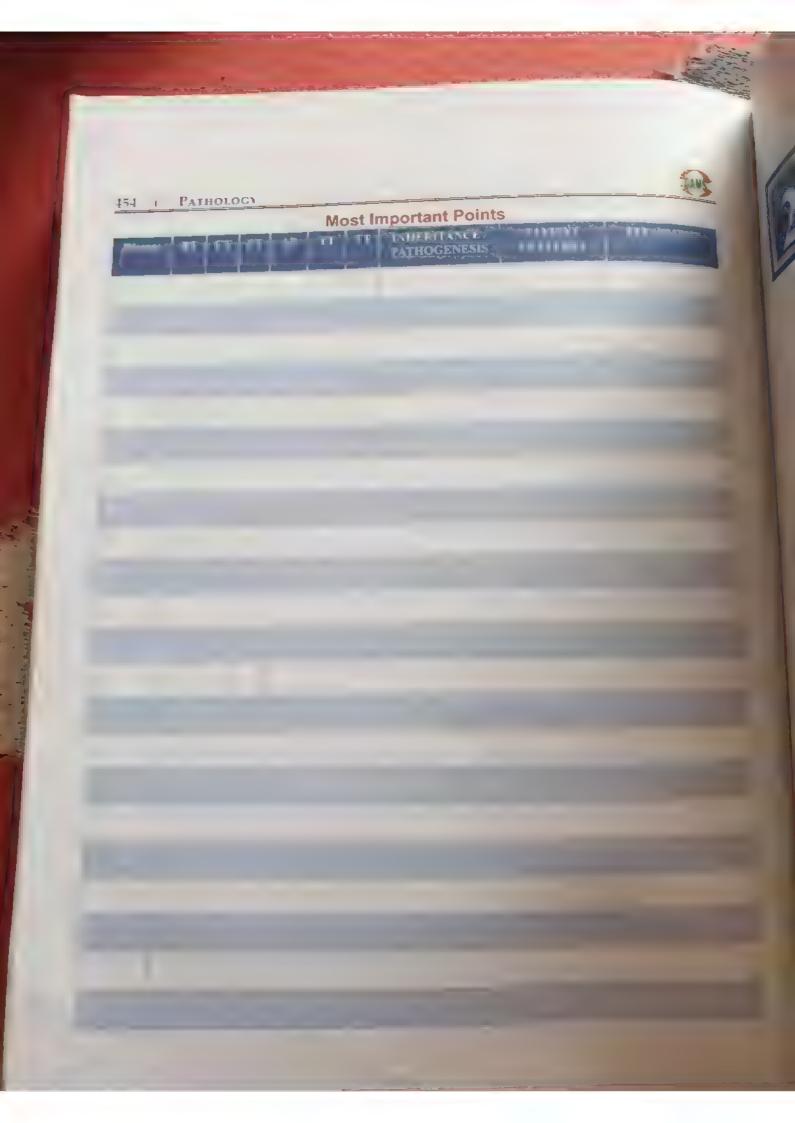
Failure to clear activated coagulation proteins (DIC)

Dysfibrinogenemia

latrogenic: Transfusion of prothrombin complex concentrates

Antifibrinolytic agents: EACA, tranexamic acid







# BLOOD BANK - IMPORTANT POINTS

### CONCEPTS

Concept 23:1: Blood Bank - Important Points

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# Concept 23.1: Blood Bank Important Points

Learning Objectives: Diagnostic criteria and treatment of all MPN

### Time Needed

J" reading 60 min 2™ reading 30 min

Donors should be between the age of 18 and 65 years.

The haemoglobin should be not less than 12.0 gm/dl or the packed cell volume The haemoglobin should be not less than 12.0 girly or the screening should be carried out by using the screening should be carried out by using (haematocrit) should be not less than 30%. The screening should be not less than 30%. The screening should be method of hemoglobin testing should be available as a reference or control.

Blood collection from donors weighing 45-55 Kg should be 350 ml blood and from those weighing 55 Kg and above should be 450 ml.

The systolic blood pressure should be between 100 and 160 mm of mercury and the diastolic pressure should be between 60-90 mm of mercury. Temperature should not exceed 37.50C/ 99.50F

Pulse should be between 60 to 100 beats per minute and regular.

### Vaccinations:

Individuals who have taken vaccination against TAB/TT/CHOLERA/ HEPATITIS-A - should be accepted if free of symptoms.

Those who have received Hepatitis B vaccination should be accepted after 7 days of vaccination.

Yellow fever/measles/polio - should be deferred for 2 weeks.

Rabies vaccination - should be deferred for 1 year.

Those bitten by any animal should be deferred for one year.

Hepatitis B Immunoglobulin-should be deferred for 1 year.

### **Donation Interval:**

The interval between two blood donations should be at least 12 weeks.

At least 48 hours must elapse after plasma pheresis or Cytapheresis before whole blood is collected from a donor.

Apheresis should be done only after 90 days of whole blood collection or in an event when red cells are not returned at the end of pheresis.

One of the following solutions should be used in the indicated volumes

Citrate-Phosphate-Dextrose (CPD) Solution.14 ml solution is required for 100 ml of

Citrate-Phosphate-Dextrose-Adenine (CPDA-1) solution.14 ml solution is required for

100 ml SAG-M/ADSOL or any approved additive solution containing saline adenine and glucose (or with mannitol) is added to packed cells after separation of plasma for storage. Temperature:

Immediately after collection, the blood should be placed at 40C to 60C + 20C except if it is used for component preparation it will be stored at 220C + 20C until the platelets



### Tests:

Test for Syphilis Each donation of whole blood should be subjected to a serological test for syphilis by VDRL / RPR Method / TPHA. Test for Viral HepatitisA test for hepatitis B (HBsAg) and hepatitis C (anti-HCV) by ELISA/Rapid test which is a validated method should be done on each unit of blood. Any technology with similar or higher sensitivity may be used additionally to improve blood safety. Screening for HIV AntibodiesAll blood units collected should be tested for HIV 1&2 antibodies using ELISA/Rapid which is a validated method. Any alternative technology with similar or higher sensitivity may be used.

Test for Malaria All blood units should be tested for malarial parasites using a validated and sensitive antigen test.

The sterility of the blood should be checked on 1% of the blood units collected or 4 per month whichever is higher.

The following colour code is used to differentiate the ABO group label

- Blood group O Blue
- Blood group A Yellow
- Blood group B Pink
- Blood group AB White

### Red blood cells:

RBCs are prepared from whole blood by centrifugation and removal of plasma The most commonly used anticoagulant preservative solution for RBCs is CPDA-1 (\*) This is supplemented with dextrose and adenine to preserve red cell ATP levels. RBCs in CPDA-1 may be stored for up to 35 days at 1-6°C.

Plasma may be stored in the liquid state at 1-6°C or it may be frozen for extended

In the liquid state at refrigerator temperature, there is loss of labile clotting factors particularly factor VIII and factor V (\*).

FFP is separated from the RBCs and is placed at -18°C within 8 hours of collection Plasma frozen within 24 hrs after phlebotomy (FP24) is manufactured similarly to FFP.

The coagulation factor content of FP24 is equivalent to FFP.

Frozen plasma may be stored for upto a year at -18°C or lower.

Before transfusion both FFP and FP24 are thawed at 37°C and must be transfused within 24 hrs.

### Cryoprecipitated Antihemophilic Factor:

Cryoprecipitated antihemophilic factor (cryoprecipitate or cryo) is the cold insoluble portion of plasma remaining after FFP has been thawed at refrigerator temperatures. It contains approximately 50% of Factor VIII and 20-40% of the fibrinogen present in

the original plasma unit (\*) Cryo also contains von Willebrand factor (vWF) and factor XIII (\*)

FDA regulations require that a unit of cryoprecipitate contain at least 80 IU of factor VIII. A unit of cryoprecipitate contains approximately 250 mg of fibrinogen (but testing for it is not required)

Currently cryo is used mainly as a source of fibrinogen (\*).



### Platelet concentrates:

Platelet concentrates are prepared from whole blood by centrifugation of platelet rich plasma and expression of platelet poor plasma Platelet concentrates must contain at least 5.5 x 10(10) platelets per unit They are stored at room temperature (20-24°C) because platelets stored at refrigerator temperature (1-6°C) have greatly diminished post transfusion survival Current FDA regulations allow PCs to be stored for upto 5 days with continuous gentle agitation (\*) At the end of storage the pH of PCs must be 6.0 or higher.

It is typically necessary to pool five or more PCs to obtain a therapeutic dose for a typical adult patient.

### Red cell transfusion guidelines:

- 1. Symptomatic anemia in a euvolemic patient.
- 2. Acute blood loss of >15% of estimated blood volume.
- 3. Preoperative Hb < 9 g/DL with expected blood loss of over 500 ml.
- 4. Hb < 7 g/dL in a critically ill patient.
- 5. Hb < 8 g/dL in a patient with acute coronary syndrome.
- 6. Hb < 10 g/dL with uremic or thrombocytopenic bleeding.
- 7. Some cases of sickle cell disease.

### Platelet transfusion guidelines:

Thrombocytopenia due to decreased production.

- 1. Stable patient : platelet count < 10,000/ microL.
- 2. Fever: platelet count < 20, 000/ microL.
- 3. Bleeding, invasive procedure or surgery: platelet count < 40,000-50,000/ microL.
- 4. Retinal or central nervous system bleeding: platelet count < 100,000/ microL Micro vascular bleeding due to platelet dysfunction.

### Plasma transfusion guidelines:

- 1. Coagulation factor deficiency, factor concentrate unavailable.
- 2. Dilutional coagulopathy.
- 3. Hemorrhage in liver disease.
- 4. DIC.
- 5. Coumadin reversal.
- 6. TTP.
- 7. Acute trauma resuscitation.

### Cryoprecipitate transfusion guidelines:

- 1. Factor VIII deficiency, factor concentrate unavailable.
- 2. Von Willebrand disease, factor concentrate unavailable.
- 3. Hypofibrinogenemia.
- 4. Factor XIII deficiency.
- 5. Uremic bleeding (DDAVP preferred).

First factor to reduce in strored blood is factor 8 followed by factor 5.

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### IMPORTANT POINTS OF Blood Banking



MISCELLANEOUS

# CONCEPTS

**○ Concept 24.1: Miscellaneous**



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# Concept 24.1: Miscellaneous

#### Time Needed

1st reading 2<sup>nd</sup> reading 30 min 15 min

Aplastic anemia

(C)assincation.

Severe

BM cellularity < 25% (or < 50% if < 30% of BM is hematopoietic cells)

AND  $\geq 2$  of the following:

 Peripheral blood neutrophil count < 0.5 X 109/L.</li> Peripheral blood platelet count < 20 X 109/L.</li>

Peripheral blood reticulocyte count < 20 X 109/L.</li>

As above, but peripheral blood neutrophil count must be < 0.2 X 10°/L Very severe

Hypocellullar BM with peripheral blood values not meeting enteria for severe aplastic Nonsevere

anemia.

	rel Delinition of Maculitide from the Compto Mill Community
Definition	
Large-Vessel Vasculitis Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and is often associated with polymyalgia rheumatica.
Takayasu's arteritis Medium-Size Vessel Vasculitis Polyarteritis nodosa (classic)	ed Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.
Kawasaki disease	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis of the arterioles, capillaries, or venules.
Small Vessel Vasculitis Wegener's granulomatosis	Arteritis involving the large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
Charg Strauss	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculity affecting small to medium-sized vessels (capillaries, venules, arterioles, and arteres Necrotizing glomerulonephritis is common
Microscopic polyangiitis	Eosinophil-rich and granulomatous inflammation involving the respiratory trace and necrotizing vasculitis affecting small to medium-sized vessels and associate with asthma and eosinophilia
Henoch-Schonlein purpura	Necrotizing vasculitis, with few or no immune deposits, affecting small vesse (capillaries, venules, or arterioles).
Essential cryoglobulinemic asculitis	Vasculitis with immunoglobulin (Ig)A-dominant immune deposits, affecting smarressels (capillaries, venules, or arterioles).
eutaneous leukocytoclastic asculitis	Vasculitis with eryoglobulin immune deposits, affecting small vessels (capillane venules, or arterioles). Typically involves skin, gut, and glomeruli, and is associated with arthralgias and arthralgias.
	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis



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	Chnical syndrome	Associated tumors and conditions
Antibody	Cerebellar degeneration	Ovary, breast
Anti-Yo	Brain and cerebellar dysfunction	SCLC, neuroblastoma
Anti-Ri (ANNA-1)  Anti-Ri (ANNA-2)  Antiamphiphysin	Opsoclonus-myoclonus Suff-man syndrome Encephalitis-neuropathy	Breast, ovary, SCLC Breast, ovary, SCLC Diabetes mellitus
Anti-VGCC	Lambert-Eaton myasthenia syndrome	SCLC

SCLC, Small cell lung cancer, VGCC, voltage gated calcium channels (anti body)

	1-1-	c		
Test	Bacterial	Viral	Fungal	Tuberculous
Opening pressure Leukocyte count Cell differential Protein Glucose CSF serum glucose ratio Lactic acid	Elevated >1000 uL  Mainly neutrophils*  Mild-marked increase  Usually <40 mg/ dL Normal-marked decrease Mild-marked increase	Usually normal <100/uL Mainly lymphocytes† Normal-mild uncrease Normal Usually normal Normal-mild increase	Variable Variable Mainly lymphocytes Increased Decreased Low Mild-moderate increase	Variable Variable Mamly lymphocytes Increased Decreased. may be <45 mg dL Low Mild-moderate increase

Nervous System				
Protein	Major diseases/disorders.			
α2-Macroglobulin β-Amyloid and τ proteins β-Microglobulin C reactive protein Fibronectin Methemoglobin Myelin basic protein Protein 14-3-3 Transferrin	Subdural hemorrhage, bacterial meningitis Alzheimer's disease Leukemia/lymphoma, Behçet's syndrome Bacterial and viral meningitis Lymphoblastic leukemia, AIDS, meningitis Mild subarachnoid subdural hemorrhage Multiple sclerosis, tumors, others Creutzfeldt-Jakob disease CSF leakage (otorrhea, rhinorrhea).			

	THE PERSON NAMED IN THE PE
	A CONTRACTOR OF STREET
Sarcoidosis	Al, B8
Good pasture's syndrome	DRB*1501, *1502
Celiac disease	DQ2, DQ8
Ankylosing spondylitis	B27*2705, *2702
Reactive arthritis	B27
Primary sclerosing cholangitis	B8
Primary membranous nephropathy	DQAI
Grave's disease	DR3
Diabetes mellitus Type 1	DR3, DR4. DQ8
Psonasis	Cw*0602
Rheumatoid arthritis	DRBI
Psoriatic arthritis	B27 and Cw6
21 Hydroxylase deficiency	BW47
Hereditary hemochromatosis	A
Systemic lupus erythematosis	DRB1*0301, *1501
SLE with anti dsDNA, anti Sm and antiphospholipid antibodies	DQ
Subacute cutaneous SLE	DR3

DR4

DR6

B51

B8, DR3, DRW52, DQA1/B1

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Hydralazine induced SLE

Procainamide induced SLE

Sjogren's syndrome

Behcet's disease

The second second	Now the same of th
Direct repair	Repairs certain types of DNA damage in a single-step reaction.
Mismatch repair	Checks for errors made when DNA is replicated. Any mispaired bases in the daughter strand are removed and replaced with the correct match.
Base excision repair	Repairs small, nonhelix-deforming adducts such as those produced by methylation, oxidation, reduction, or base fragmentation by ionizing radiation
Nucleotide excision repair	Removes bulky DNA adducts such as thymine dimers and certain photoproducts as well as chemical adducts and cross-links.
Double-strand break repair	Repairs double-strand breaks that result from physiologic processes or from ionizing radiation and oxidative insults.

	Kes Featu	res of Hodgkin Lym	phomas	
Lymphoma	presentation	Morphology	Cell surface markers	Prognosis
Nodular.	years, with peripheral tymphadenopathy.	Mononuclear cells with convoluted nuclei (popcorn or LHS cell) loosely aggregated in nodules of small & cells.	CD45, CD20, bcl-6,s J-chain, Oct-2, BOB.1, EBV absent in LP cells.	Excellent for stages 1, II
Nodular sclerosis	M - F, <30 years with mediastinal mass, occasional spleen or lung involvement; 40% have B symptoms; most patients present with stage II disease.	Broad bands of collagen, nodules of lymphoid tissue with aggregates of HRS cells and lacunar cells, multinucleated variants.	CD15, CD30, CD45-EBV in 1%- 40%.	Good with systemic therapy.
Mixed cellularity	M > F; median age, 38 years; peripheral lymphadenopathy common, spleen. BM, B symptoms common, patients often stage III or IV	Classic HRS cells in mixture of lymphocytes, plasma cells, eosinophils, histiocytes.	CD15, CD30, CD45-EBV in 75%.	Good with systemic therapy
Lymphocyte depletion.	M > F; median age, 30-37 years; B symptoms, advanced stage common; associated with HIV.	Classic HRS cells common with paucity of background lymphocytes; pleomorphic HRS cells mimus sarcoma	CD15, CD30, CD45- EBV pos in HIV- affected patients.	Associated with advanced stage.
Lymphocyte-rich classical	M > F, older age: peripheral lymphadenopath B symptoms rare most patients with stage 1 or 1 disease.	Scattered classic HRS cells amor y, numerous small tymphocytes; nodular growth	J chain absent. EBV in 40%-75	, NEFFE

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Acute glomerulonephi	Gross hematuria "smok	<ul> <li>Erythrocyte and blood casts Epithelial casts Hyaline and granular casts</li> <li>Neutrophils</li> <li>Erythrocytes</li> </ul>
Chronic glomerulonephr	Hematuria Proteinuria	Granular and waxy casts Occasional blood casts Lipid dorplets.
Acute pyelonepl		Numerous neutrophils (many in clumps) Few lymphocytes and histocytes  Leukocyte casts  Renal epithelial cells  Epithelial casts  Granular and waxy casts  Bacteria.
Chronic pyelonephritis	Occasional proteinuria	Leukocytes Broad waxy casts Granular and epithelial cells Occasional leukocyte cysts Bacteria Erythrocytes.
Nephrotic syndrot	ne : Protemuria	Fatty and waxy casts.  Cellular and granular casts.  Oval fat bodies and/or vacuolated renal epithelial cells occurring single or as cellular cluters.
Acute tubular necrosis	Hematuria Occasional proteinuria,	Necrotic or degenerate renal epithelial cells.  Neutrophils and erythrocytes.  Granular and epithelial casts.  Waxy casts.  Board casts.  Epithelial tissue fragment.
Cystitis	Hematuria	Numerous leukocytes. Erythrocytes. Transitional epithelial cells occurring singly or as fragments. Histiocytes and giant cells. Bacteria. Absence of casts.
Dysuria-pyuria yndrome.	Slightly turbid	Numerous leukocytes, bacteria. Erythrocytes. No casts.
cute renal allograft gection (lower ephrosis).	Hematuria Occasional proteinuria.	Renal epithelial cells. Lymphocytes and plasma cells. Neutrophils. Renal epithelial casts. Renal epithelial fragments. Granular blodds and
inary tract oplasia	Hematuria	Granular, bloddy, and waxy casts.  Atypical mononuclear cells with enlarged irregular hyperchromatical and secretary.
seases	Macroscopic urinalysis	Microscopic urinalysis. Neutrophils. Erythrocytes.
al infection	Hematuria Occasional proteinuria.	Transitional epithelial cells.  Enlarged mononuclear cells and/or multinucleated cells with prominent intranuclear and/or cytoplasmic inclusions Neutrophils.  Lymphocytes and plasma cells.  Erythrocytes.

The second second	Managal	Chalment and Feral Fundames in		
Finding	Normal	Obstruction to bile flow.	Hemolysis, hemolytic anemia.	Liver damage, hepatitis, cholestasis
t rmary bilirubin	Absent	Increased, dark urine.	Absent	Increased early.
t rmary probilinogen	Present	Neoplasm low or absent; gallstones-variable	Increased	Decreased early, increased late
Fecal color	Dark	Pale; intermittent with gallstones in common bile duct; persistent with neoplasm in duct or pancreas.	Dark	Pale early and dark late in hepatitis; pale with cholestasis.

#### FRV associations

Mononucleosis-type illness.

Hodgkin lymphoma: MC > LR > NS; LD seen in HIV patients.

Immunodeficiency-associated lymphoproliferative disorders.

Posttransplant lymphoproliferative disorders.

Some DLBCL cases (associated w/inflammations, in elderly).

Lymphomatoid granulosis.

Primary effusion lymphoma.

EBV+ lymphoproliferative disorders of childhood.

Burkitt lymphoma (endemic and HIV associated).

Nasal NK-T cell lymphoma.

Angioimmunoblastic lymphoma.

Plasmablastic lymphoma.

### (pudehous for Nears 1)

#### **RBC Transfusion:**

Hct <30% with supplemental O2 <35% or mechanical ventilation with MAP <6 cm H2O.

Hct <35% with supplemental O2 >35% or mechanical ventilation with MAP >6 cm H2O.

Het <45% with cyanotic congenital heart disease or extracorporeal oxygenation.

#### Plasma Transfusion:

Coagulation factor deficiency, factor concentrate unavailable.

Disseminated intravascular coagulation (DIC).

Platelet count < 30,000  $\mu$ L in term infant with platelet production failure Platelet count < 50,000/ $\mu$ L in

stable premature infant Platelet count < 100,000 µL in unstable premature infant.

Symptomatic anemia in a euvolemic patient

Acute blood loss of >15% of estimated blood volume.

Preoperative Hb <9.0 g/dL with expected blood loss >500 mL Hb <7.0 g/dL in a critically ill patient.

Hb <8.0 g/dL in a patient with an acute coronary syndrome.

Hb <10.0 g/dL with uremic or thrombocytopenic bleeding.

Sickle cell disease:

Acute sequestration: Hb <5.0 g/dL or decrease of 20% from baseline.

Acute chest syndrome: Target Hb = 10 g/dL, HbS

fraction <30% Stroke prophylaxis: Target HbS fraction <30% General anesthesia: Target Hb = 10.0 g/dL, HbS fraction <60%

- Factor VIII deficiency, factor concentrate unavailable von Willebrand disease, factor concentrate unavariable.
- Hypofibrinogenemia.
- Factor XIII deficiency.
- Uremic bleeding (DDAVP preferred).
- Topical fibrin sealant (commercial product preferred).

#### Salient features of Germ cell and sex cord stromal tumors of ovary:

Naples		1 jong	Morphologic Features	Benavior
Germ Cell Origin				
Dysgerminoma	Second to third decade of life Occur with gonadal dysgenesis.	Unilateral in 80%- 90%	Counterpart of testicular seminoma sheets or cords of large clear cells Stroma may contain lymphocytes and occasional granulomas.	All malignant but only one-third metastasize; all radiosensitive, 80% cure rate.
Choriocarcinoma	First 3 decades of life	Unilateral	Identical to placental tumor Two types of epithelial cells: cytotrophoblast and syncytiotrophoblast.	Metastasizes early and widely Primary focus may degenerate. leaving only metastases Resistant to chemotherapy.

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Sex Cord Tumors				
Granulosa-theca cell	Most postmenopausal, but may occur at any age.	Unilateral	Composed of mixture of cuboidal granulosa cells and spindled or plump lipid-laden theca cells  Granulosa elements may recapitulate ovarian follicle as Cell-Exner bodies.	May elaborate large amounts of estrogen Granulosa element may be malignant (5%-25%).
Thecoma-fibroma.	Any age	Unilateral	Yellow (lipid-laden) plump thecal cell.	Most hormonally inactive About 40% produce ascites and hydrothorax (Meigs syndrome) Rarely malignate.
Sertoli-Leydig cell	All ages	Unılateral	Recapitulates development of testis with tubules or cords and plump pink Sertoli cells.	Many masculinizing of defeminizing Rarely malignant.
Metastases to Ovar	y Older ages	Mostly bilateral	Anaplastic tumor cells, cords, glands, dispersed through fibrous background Cells may be "signet ring" mucin-secreting.	Primaries are gastrointestinal tract (Krukenberg tumors), breast, and lung.

# Factors associated with risk of invasive carcinoma in breast:

Factor		
- Actor	Riska	
Women with no risk factors	1.0	3%
First-degree relatives(s) with breast cancerb	1.2-9.0	4%-30%
Germline tumor suppressor gene mutation (e.g BRCA/mutation)	2.0-45.0	6% to ~90%
Menstrual History	13	4%
Age at menarche <12 years	1 5-2.0	5%-6%
Age at menopause >55 years		
Pregnancy	-	

470 1 PATHOLOGY	<u> </u>	
First Irve birth <20 years (protective)	0.5	1 6%
First live birth 20-35 years	11.5-2.0	15 6
First live birth >35 years	2.0-3.0	6%-10%
Never pregnant (nulliparous)	\ 3.0	110%
Breast feeding (slightly protective)	0.8	2.6%
Benign Breast ssDisease		
Proliferative disease without atypia	1.5-2.0	> 0-6
Proliferative disease with atypia (ALH and ADH)	4.0-5.0	13%-17%
Carcinoma in situ (ductal or lobular)	8.0-10.0	250 6 301 6
Lonizing radiation	1.1-1.4	3.6%-4 6%
Mammographic density	3.0-7.0	10%-23%
Postmenopausal obesity and weight gain	1.1-3.0	3.6%-10%
Postmenopausal hormone replacement	1.1-3.0	3.6%-10%
Alcohol consumption	1.1-1.4	3.6%-4.6%

## Summary of the major biological types of breast cancer:

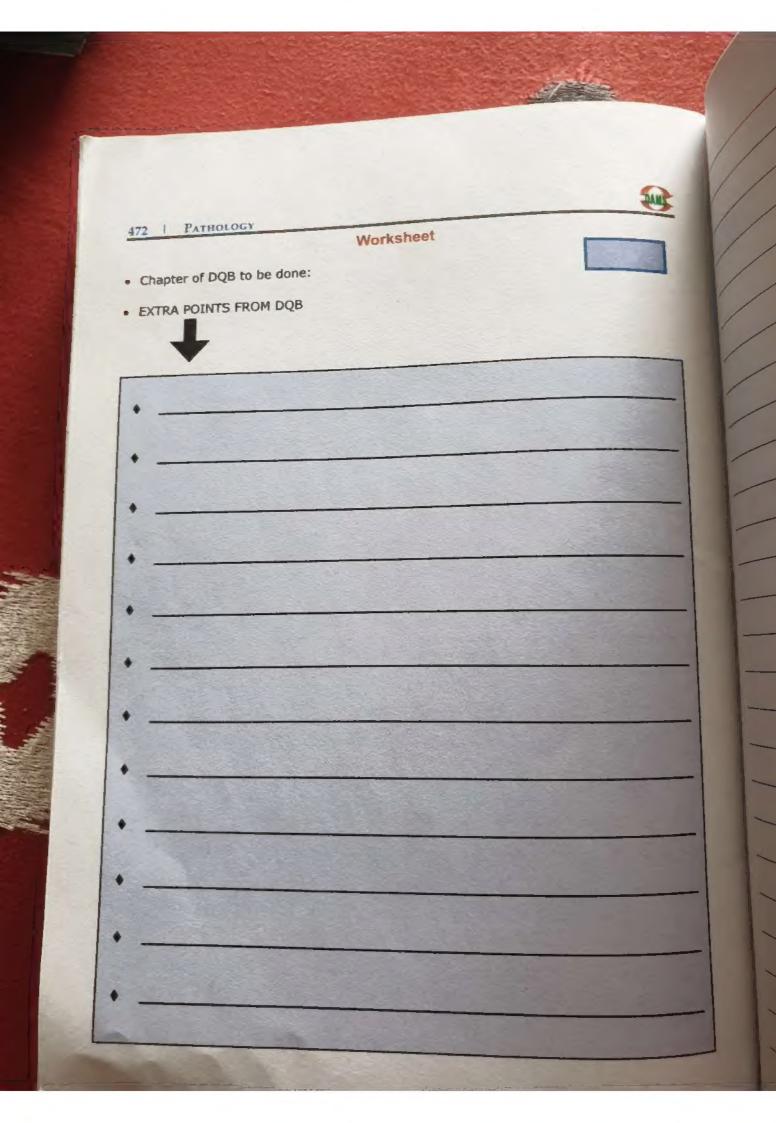
Feature	ER Positive / Liz KZ	HER2 Fosnive (ER	Triple Negative
Overall frequency	50%-65%	20%	15%
Typical patient groups.	Older women; men; cancers detected by screening; germline BRCA2 mutation carries,	Young women, germline TP53 mutation carries.	Young women: germline BRCA/ mutation carries.
Ethnicity			
European/American	70%	18%	12%
African/American	52%	22%	26%
Hispanic	60%	24%	16%
Asian, Pacific Islander	63%	26° o	11%
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	Lower grade (<10%), higher grade (10%)	ER positive (15%), ER negative (>30%)	30%
Timing of relapse	May be late (>10 years after diagnosis)	Usually short (<10 years after diagnosis)	Usually short (<8 years after diagnosis

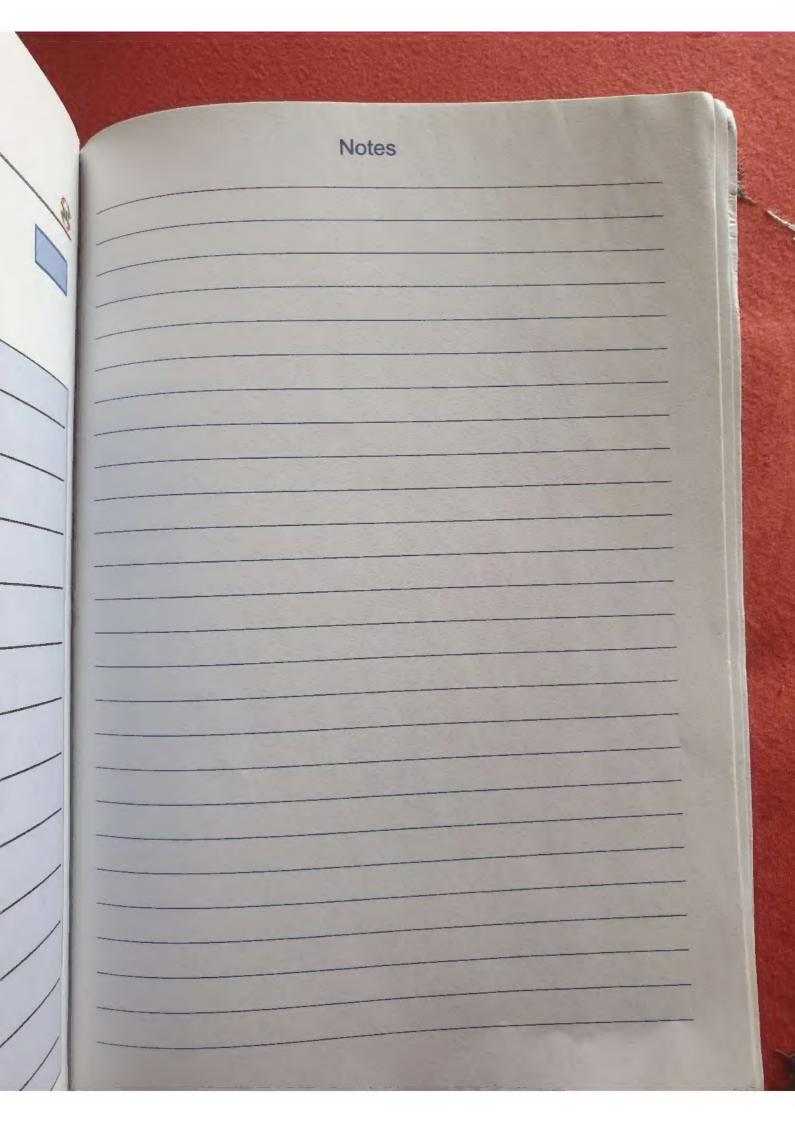


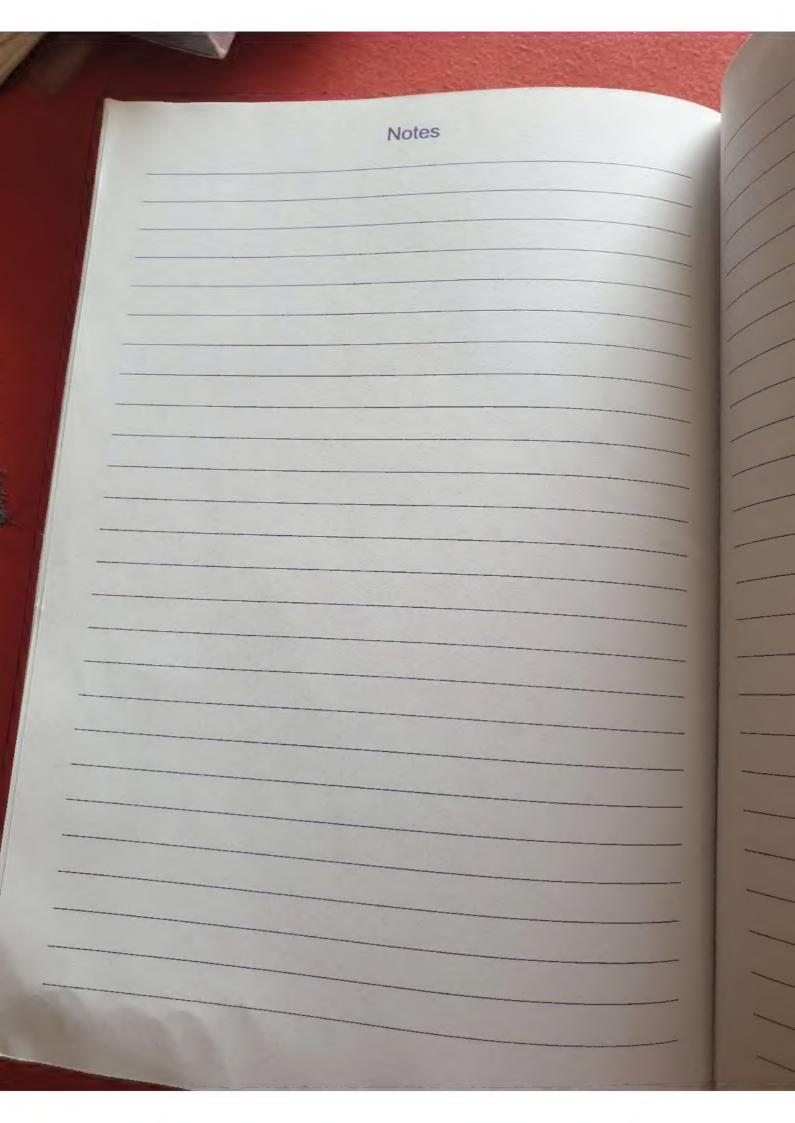
Metastatic sites	Bone (70%), viscera (25%), brain (<10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Similar group defined by Mrna profiling	Luminal A (low grade), luminal B (high grade).	Luminal B (ER positive), HER2-enriched (ER negative).	Basal-like.
Common special histologic types.	Lobular, tubular, mucinous, papıllary.	Apocrine, micropapilary.	Carcinoma with medullary features.
Common somatic mutations	PIK3CA (40%), TP53 (26%)	TP53 (75%), PIK3CA (40%)	TP53 (85%)

# Targetted treatment of breast cancer:

Targel			
R	Estrogen deprivation (oophorectomy. Aromatase inhibitors) Blockage of ER (tamoxifen).	IHC for nuclear ER.	Effective cytostatic (but not cytotoxic) therapy for ER-positive cancer.
IER2	Antibodies to HER2 Cytotoxic therapy linked to HER2 antibody Tyrosine kinase inhibitors.	IHC for membrane HER2 ISH for HER2 gene amplification.	Effective for HER2- positive cancers.
Susceptibility to DNA damage resulting from BRAC I and BRAC2 mutations that cause defect in HRR.	Chemotherapy with agents causing DNA damage that requires HRR (e.g. platinum agents) Inhibition of alternative DNA repair pathway (poly-ADS ribose polymerase or PARA	Sequencing of BRCAI and BRCA2.	May be effective for carcinomas arising in patients with germline BRCA / or 2 mustations or cancers with somatic loss of BRCA function.
Pl3K/AKT pathway	inhibitors). Inhibitions or proteins in the pathway.	Activating mutations or pathway activation-not yet validated.	>80% of breast cancers have alternations in thi pathway Effectivencess or treatment not yel demonstrated.
Immune checkpoint proteins.	Blocking antibodies to PD-LI, PD-I, and other immune checkpoint proteins.	IHC for immune checkpoint proteins-not yet validated.	Under investigation in patients with triplenegative breast cancer









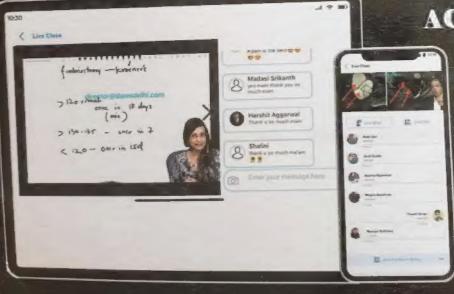
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